Volume 94, Number 6, June 1987

7.4.88

British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten

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Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications
BJOGAS 94(6) 497–608 1987 ISSN 0306-5456

British Journal of Obstetrics and Gynaecology

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CUH-H06158-16-P2540
P25405

British Journal of Obstetrics and Gynaecology

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Edited by Frank E. Hytten

Volume 94
1987

Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications

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Published on behalf of the
Royal College of Obstetricians and Gynaecologists
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Printed in Great Britain
by Headley Brothers Ltd
The Invicta Press
Ashford, Kent and London

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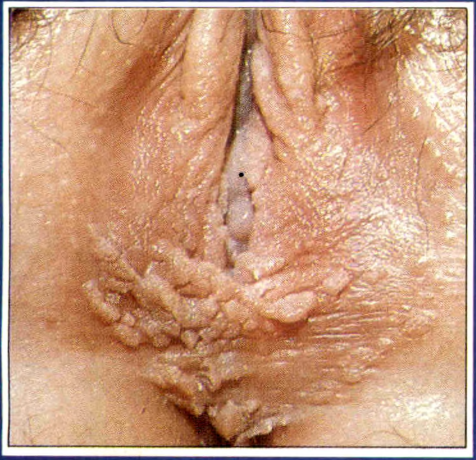

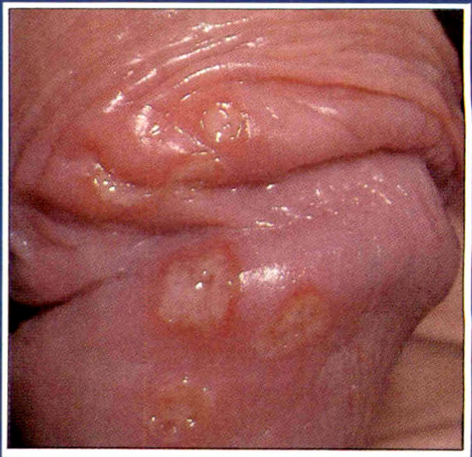

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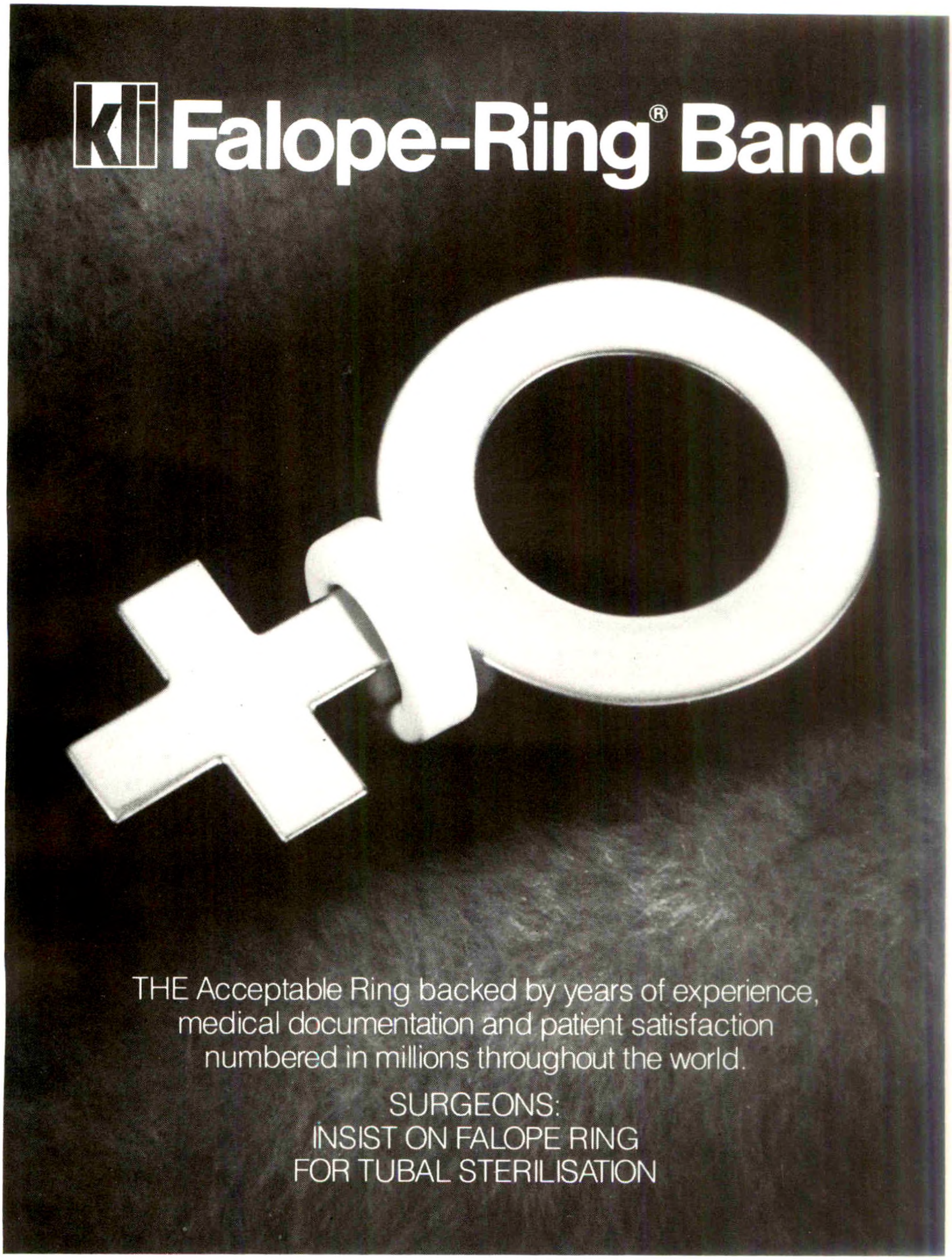

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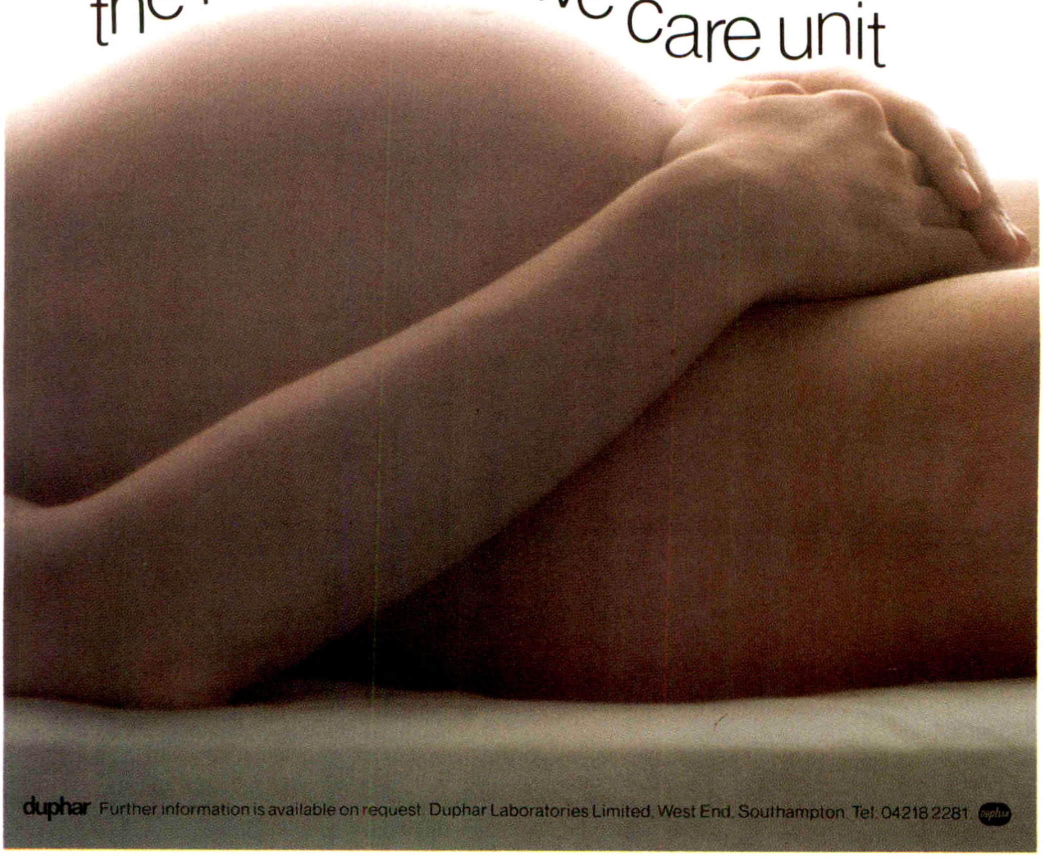

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British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 497–498

COMMENTARY

Which blood pressure?

It is over 100 years since the high blood pressure in eclampsia was first investigated, but it was not until 1903 that the value of sphygmomanometry in obstetrics was reported in the English language. Two enterprising housemen at the Johns Hopkins Hospital, using the recently introduced Riva–Rocci machine to make observations in several conditions, including pregnancy, stressed the value of these readings in foreseeing the onset of eclamptic fits. Taking the blood pressure became an integral part of antenatal care, and the systolic level was used as an index of the severity of pre-eclampsia, no importance being attached to a rise in the diastolic pressure alone (Brown 1944).

There was a gradual acceptance of the use of the diastolic reading as well, which was thought to be less subject to variation from outside causes than the systolic (Hughes 1951). Nelson (1955) stated that the hypertension of pre-eclampsia was diastolic in nature and chose the value of 90 mmHg as the lower limit of abnormality, stressing that this was entirely arbitrary, being a compromise between clinical experience and the dictates of his epidemiological investigations.

There has been an unfortunate progression from this position to one where a diastolic pressure of 90 mmHg is taken as the sole criterion for the diagnosis of abnormality and, as an extension of this, the height of the diastolic pressure alone is used in formulating management. Taking this approach to its illogical conclusion means that an eclamptic with a blood pressure of 220/10 mmHg (which has been recorded) does not need hypotensive therapy.

Page (1972) has championed the use of mean arterial pressure (MAP) as, physiologically, this is the important determinate. It is calculated as

MAP = diastolic + one-third pulse pressure

An acute marked elevation of the MAP will cause a higher pulse pressure with a proportionately greater increase in the systolic than in the diastolic pressure.

The effects of a raised blood pressure are mediated at the level of the arterioles and smaller vessels. The arterioles constitute half of the total resistance to flow and there is a transition from pulsatile to non-pulsatile pressure with a fall in the MAP from about 75 to 35 mmHg. A steep, rapid rise in pressure in the cerebral circulation may break through the myogenic autoregulation causing the hypertensive encephalopathy of eclampsia or frank cerebral haemorrhage, and a similar mechanism may be a factor in the production of some cases of placental abruption.

One major disadvantage in the use of the diastolic pressure is the lack of a uniform end-point in its determination. In 1939 the American Heart Association and the Cardiac Society of Great Britain and Ireland stated that the point of muffling was more reliable than that of disappearance of the Korotkoff sounds, this decision being reversed in 1951 and changed yet again in 1967. The current advice (Kirkendall *et al.* 1981) is that the point of complete cessation should be used, but both values should be recorded for both arms; however, the point of muffling should be used in children and in adults with hyperkinetic states. It is not mentioned that pregnancy is a hyperkinetic state in which the altered haemodynamics often result in blood pressure sounds on auscultation persisting until zero pressure is reached in the cuff. Most British clinicians have kept to the original 1939 recommendation which means that the conventional dividing line between normal and abnormal of 140/90 mmHg American style equates with a level of 140/100 British style.

The use of the diastolic blood pressure level in relation to vascular disease has been disputed by Fisher (1985). He has questioned the evidence establishing the ascendancy of diastolic recordings over the systolic and advised taking the systolic pressure alone. The use of the diastolic value alone as an index of hypertensive states in pregnancy has little to commend it apart from its appearance in published work over the last 30 years. MAP has not found general acceptance, perhaps because it has to be calculated, and it does not overcome the faults associated with the measurement of diastolic pressure.

Use of the systolic pressure alone would have much to commend it. In pre-eclampsia the systolic pressure, rather than the diastolic, is the factor which significantly influences the prognosis for the fetus (Tervilä *et al.* 1973); in chronic hypertensive disease the systolic pressure correlates well with the fetal outlook (Chesley & Annitto 1947); in the diagnosis of pre-eclampsia by a rise in the blood pressure the diastolic values are no more sensitive than the systolic (Redman 1984).

Apart from polite murmurings of approval, Fisher's advice to take the systolic pressure alone has made no headway, and obstetricians are unlikely to rush in where physicians fear to tread. We should at least recognize the drawbacks associated with the use of the diastolic pressure alone and give due deference to the value of the systolic pressure.

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British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 499–506

Stroke and minute distance in pregnancy: a longitudinal study using Doppler ultrasound

F. M. McLENNAN, N. E. HAITES, J. M. RAWLES

Summary. Using Doppler ultrasound directed at the aortic arch, stroke and minute distance were measured in 45 normal singleton pregnancies and compared with 42 controls. In the non-pregnant controls, stroke distance was 5% more in the supine than in the left lateral position ($P<0{\cdot}01$) and during pregnancy this relativity was maintained until 36 weeks gestation. In the supine and left lateral positions respectively, stroke distance was increased by 8% (both) at 4 weeks ($P<0{\cdot}05$ and NS), by 14 and 11% at 8 weeks ($P<0{\cdot}001$ and $P<0{\cdot}01$) and showed a maximum increase of 21 and 20% at 16 weeks gestation (both $P<0{\cdot}001$). At 40 weeks, supine stroke distance was 14% less than the non-pregnant control value ($P<0{\cdot}001$), and 6% less than the value in the left lateral position ($P<0{\cdot}05$), which was itself not significantly different from that in the non-pregnant controls. The maximum increase of heart rate was at 32 weeks, by 24% in the supine and by 19% in the left lateral position (both $P<0{\cdot}001$). Minute distance was maximally increased by 37% in the supine at 16 weeks ($P<0{\cdot}001$) and by 30% in the left lateral position at 24 weeks ($P<0{\cdot}001$). Thereafter, minute distance, measured in both positions, declined until at 40 weeks it was not significantly different from the non-pregnant control value.

'A de Swiet (1980) wrote that wholly satisfactory study [of cardiac output in pregnancy] has yet to be made: we can but record that Walters *et al.* [1966] were not aware of the supine effect, that Pyörälä [1966] and Ueland *et al.* [1969] made no measurement in early pregnancy and that Lees *et al.* [1967] had no matching non-pregnant value. Yet the circumstantial evidence is strong that for the normal pregnant woman at rest, but not lying on her back, cardiac output rises within the first ten weeks of pregnancy by about 1·5 l/min and that rise is maintained for the remainder of the pregnancy.'

Since that was written the position with regard to our knowledge of cardiac output in pregnancy has not materially changed but new non-invasive methods of measuring cardiac output have been developed. Using impedance cardiography to measure cardiac output, Atkins *et al.* (1981*a*) reported a fall in stroke volume and cardiac output from a maximum in mid-pregnancy to a value at term that was less than that before pregnancy, challenging the textbook opinion quoted above.

Thus, there are three questions outstanding about cardiac output in pregnancy: the time of onset of the increase in cardiac output, the relative magnitude of cardiac output measured in the supine and left lateral positions at various stages of pregnancy, and the behaviour of cardiac output in the third trimester.

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The study of volumetric cardiac output has been hampered by the technical difficulty and invasive nature of the measurement. However, recently we have suggested that cardiac output can be considered as a distance (Haites *et al.* 1984), with the advantage that it may then be measured simply and non-invasively using Doppler ultrasound. The basic measurement is of stroke distance, the systolic velocity-integral of aortic blood flow; its product with heart rate gives minute distance. Stroke and minute distance are the linear analogues of stroke volume and cardiac output respectively (Haites *et al.* 1985). Minute distance is related to volumetric cardiac output by aortic cross-sectional area, just as cardiac index is related to volumetric cardiac output by body surface area.

In this paper we present results of a longitudinal study of stroke and minute distances in singleton pregnancies.

Patients and methods

Non-pregnant controls

All patients were under the care of an obstetrician with a special interest in infertility. This gave us the opportunity to make multiple measurements in a group of 42 non-pregnant women, mean age 29 (SD 3·6) range 22–37 years, who were attending the infertility clinic. For each control subject a mean value was calculated from an average of 2·9 measurements, which were made under conditions identical to those during pregnancy. Mean values for the control group were calculated from the mean values for each subject. In six pregnancies, measurements were made before, or about the time of, conception and then through pregnancy to term and postpartum, these patients providing their own non-pregnant control values which are included in the control group. Patients recruited into control and pregnancy groups were consecutive, and their numbers were dictated by the duration of a research fellowship held by the first author.

Singleton pregnancies

There were 45 women included in this group, 23 of them had been recruited to the study by 8 weeks gestation, 34 by 20 weeks, and 40 by 32 weeks; all had measurements in the first week after delivery in hospital and in 35 women measurements were repeated at about 6 weeks postpartum at an out-patient visit. The mean maternal age of the group measured at 8 weeks gestation was 28·3 (SD 4·2) range 22–37 years, and of the group measured at delivery 28·6 (SD 4·9) range 21–40 years, and the mean gestational age on recruitment was 13·7 weeks. Thirty subjects were primiparous, 15 multiparous. All pregnancies were uncomplicated and resulted in live births at between 32 and 42 weeks gestation (mean 39·4, SD 2·0). The gestational age was calculated from the first day of the last menstrual period or, in oligomenorrhoeic patients, by ultrasound scan. On average, in each subject, measurements were made on 9·1 occasions before delivery at intervals of 3·2 weeks, and on 3·5 occasions in the first week postpartum.

Measurement protocol

Patients in this study attended the antenatal clinic as clinically indicated, and the visits were no more frequent or regular than for other patients. At each attendance, after the clinical consultation, subjects were asked to wait, seated in a waiting area outside the consultation room. After a few minutes, each patient then walked into an adjoining room and lay supine on an examination couch for 2 or 3 min before the first (supine) ultrasound measurement was made. She then turned to the left lateral position and after a wait of about 1 min the second (left lateral) recording was made. The rest periods before the measurements were not standardized and the total time taken for the two measurements including the waiting period was less than 10 min.

Measurements were made with the Transcutaneous Aortic Velograph (Muirhead Medical), as described previously (Haites *et al.* 1985). A broad beam of continuous wave ultrasound at 2 MHz is directed at the aortic arch from the suprasternal notch. Correct positioning of the transducer is aided by an audible signal and by a paper record of spectral analysis of back-scattered ultrasound, produced in real time. The recordings were made without regard to the phase of respiration which continued spontaneously, and were of sufficient duration to include at least one complete respiratory cycle. The records were subsequently digitized by another observer using a Summagraphics Bit-Pad and Sirius microcomputer with our own program. Stroke distance, heart rate, and minute

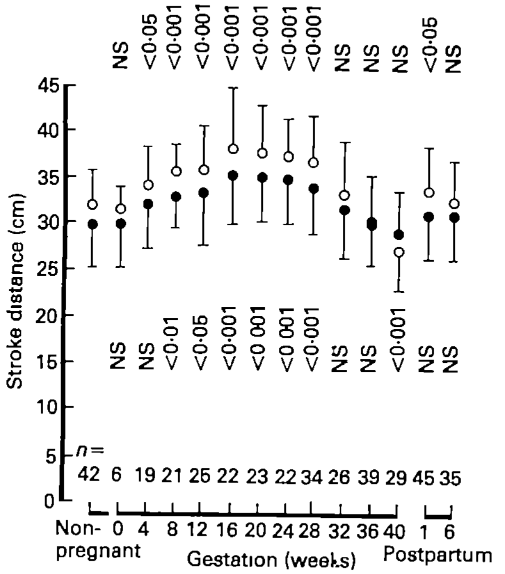

Fig. 1. Mean (±SD) stroke distance in supine (○) and left lateral (●) positions in non-pregnant control subjects and during pregnancy. *n*, Number of subjects Probability values refer to comparison with non-pregnant control values in the same posture.

distance were averaged from a mean of 13·0 (SD 2·4, range 7–22) successive beats of each recording. The results were transferred directly to a dBaseII file, so that at each digitizing session the operator was unaware of previous results.

The beat-to-beat coefficient of variation is about 9% for stroke distance, 6% for heart rate, and 8% for minute distance and the corresponding standard errors of the mean derived from 13 beat recordings are <2·5% (McLennan *et al.* 1986) The overall repeatability of the measurement of stroke and minute distance and its evaluation by planimetry is about 5% (McLennan *et al.* 1986).

Statistical methods

For each patient, values of stroke distance, heart rate and minute distance in supine and left lateral positions were derived at 4-weekly intervals throughout pregnancy from recordings taken within 2 weeks of the nominal gestational age. Thus, stroke distance at 4 weeks gestation is the mean of measurements made between >2 and 6 weeks gestation. Measurements in the first 7 days postpartum were averaged to give the 1 week postpartum value, and measurements made between 4 and 8 weeks after delivery gave the 6 week postpartum value.

Comparison of supine and left lateral measurements was by Student's paired *t*-test, otherwise the unpaired *t*-test was used.

Results

Effect of posture in the control group

Comparing measurements in the supine with the left lateral positions, stroke distance was 5·4% more ($P<0·01$), heart rate 3·6% less ($P<0·001$) and minute distance, the product of the previous two measurements, not significantly different.

Effect of age

There was no significant relation between age and stroke distance in the non-pregnant controls ($r = -0·25$) or at any gestational age during pregnancy.

Effect of posture in pregnancy

Except for the measurements at 36 and 40 weeks, mean values of stroke distance on all other occasions before and after delivery were greater in the supine than in the left lateral position, the differences were statistically signifi-

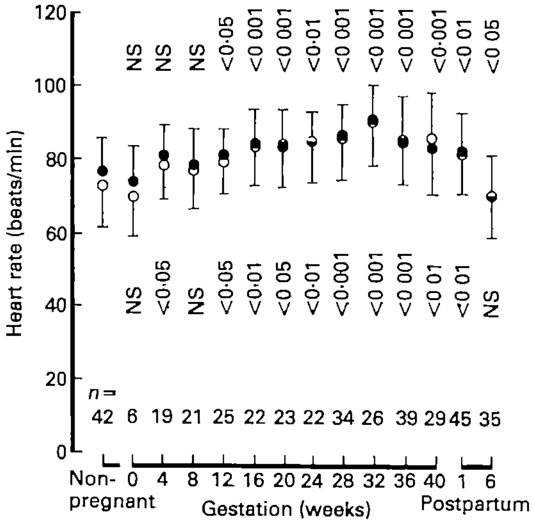

Fig. 2. Mean (±SD) heart rate in supine (○) and left lateral (●) positions in non-pregnant control subjects and during pregnancy See also legend Fig 1

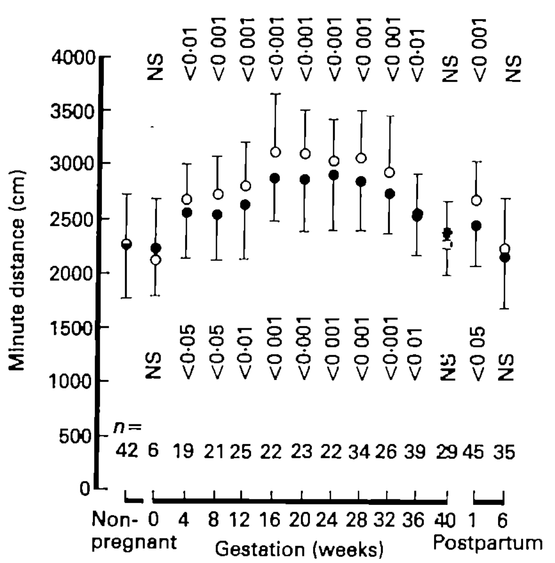

Fig. 3. Mean (±SD) minute distance in supine (○) and left lateral (●) positions in non-pregnant control subjects and during pregnancy See also legend Fig. 1.

cant, except at 32 weeks. At 40 weeks, stroke distance was 6·0% less in the supine than in the left lateral position ($P<0·05$), but in the first postpartum week the situation was reversed and the supine value again exceeded the left lateral value by 9·8% ($P<0·001$) (Fig. 1).

Generally, the effect of the position of measurement on heart rate was the reverse of its effect on stroke distance, though proportionately less (Fig. 2). As a consequence, minute distance (Fig. 3) was less affected than stroke distance by the position of measurement; nevertheless, minute distance was significantly more in the supine than in the left lateral position at between 8 and 20 weeks and at 28 weeks gestation. At 36 and 40 weeks the values were almost identical, and in the first postpartum week it was 7·9% more in the supine position ($P<0·001$)

Effect of gestational age

Measured respectively in the supine and left lateral positions, and compared with non-pregnant control values, stroke distance was increased by 8·0 and 7·8% ($P<0·05$ and NS) at 4 weeks and by 13·5 and 10·8% at 8 weeks gestation ($P<0·001$ and $P<0·01$). The maximal increases were 20·8 and 19·7% respectively, both at 16 weeks (both $P<0·001$). From then until term stroke distance declined, so that at 40 weeks stroke distance was −14·4% and −3·7% compared with control values ($P<0·001$ and NS) (Fig. 1).

In the first postpartum week stroke distance was increased by 7·7 and 3·7% ($P<0·05$ and NS), but was not significantly different from control values at 6 weeks postpartum (both NS).

Heart rate also increased early in gestation and reached a maximum value of 89 beats in both supine and left lateral positions at 32 weeks (both $P<0·001$), later than the maximum value for stroke distance which occurred at 16 weeks (Fig. 2).

In the supine and left lateral positions respectively, minute distance was increased by 16·4 and 14·8% at 4 weeks ($P<0·01$ and $P<0·05$), and achieved maximum increases of 37·0% in the supine and 30·2% in the left lateral position (both $P<0·001$) at 16 and 24 weeks respectively. At 40 weeks. minute distance was not significantly different from the control value in either position In the first postpartum week, minute distance was again increased, by 17·6 and 10·1% ($P<0·001$ and $P<0·05$), but by 6 weeks postpartum it was within 7% of the control values (both NS).

Discussion

Relation between Doppler measurements and cardiac output

Left ventricular stroke volume may be calculated as the product of aortic cross-sectional area and the systolic velocity-integral of aortic blood flow, or stroke distance. The measurement of stroke distance is highly reproducible but that of aortic cross-sectional area is not. However, stroke distance, being effectively stroke volume divided by aortic cross-sectional area, is analogous to stroke index (stroke volume divided by body surface area). Constancy of aortic size is an important requirement if stroke distance is to be used by itself as a measure of cardiac output; any increase in aortic cross-sectional area would result in a lower blood velocity for the same flow rate Blood pressure is an obvious factor that might alter aortic diameter, but the compliance of the aorta is such that the effect of the minor fall in blood pressure that occurs during the course of normal pregnancy would have a negligible effect on aortic size (Towfiq *et al.* 1986).

More serious is the possibility that the aorta dilates in late pregnancy, leading to a reduction in stroke distance in both supine and left lateral positions between the second and third trimesters. However, a fall of volumetric cardiac output in the third trimester, measured by methods that are independent of aortic size, has been widely reported, whereas there are few observations of aortic dilatation in late pregnancy. We would have to postulate increases of systolic aortic cross-sectional area of 30–45% in single and multiple pregnancies, corresponding to increases in diameter of 15–20% between second and third trimesters. Further, for the return of minute distance to normal values by 6 weeks postpartum, a similar reduction of aortic size during that period would be needed. It is unlikely that changes in aortic size of this magnitude could have gone unnoticed. Katz *et al.* (1978) measured end-diastolic aortic root diameter in each trimester and at 6–12 weeks postpartum. Compared with the postpartum measurement aortic cross-sectional area was increased by 0, 13·3 and 16·9% in the left lateral position, and by 0, 3·5 and 5·9% supine, and none of these changes was statistically significant. No significant changes of aortic root diameter during pregnancy or postpartum were reported in a recent echocardiographic study (Meyenburg 1985). On the other hand, Hart *et al.* (1986) reported a 30·7% fall of mean aortic cross-sectional area between term and 3 months postpartum, recorded in the left lateral position. Further work is needed in this area, but a change of aortic size of this magnitude is unlikely to occur entirely between second and third trimesters. Therefore, if this recent observation is confirmed, our conclusions about the increase of aortic blood flow in early pregnancy and the effect of posture will not be materially altered, and on the available evidence, the third trimester fall of minute distance that we describe could not be entirely attributed to aortic dilatation.

A second assumption underlying the use of velocity measurements to assess aortic blood flow is that the flow profile is not altered with a change of flow rate. Alteration of the flow profile would impair the correlation between stroke distance and stroke volume within subjects In studies in which changes in stroke distance have been compared with changes in stroke volume the deviations from exact proportionality have ranged from 9–13% (Light *et al.* 1986). There is no direct information on constancy of the flow profile in pregnancy, but when stroke volume was experimentally increased by dobutamine, a situation somewhat akin to that in pregnancy, Doppler data correlated closely with results from thermodilution (Ihlen *et al.* 1985).

Measurement of cardiac output per minute entails a sampling error if it is based on a time-sample less than a minute; it should be noted that this applies to thermodilution as well as Doppler techniques (Mackenzie *et al.* 1986). By averaging the measurements of about a dozen beats occurring in a time-sample that includes at least one respiratory cycle, the sampling error is kept acceptably low (McLennan *et al.* 1986).

Critique of study design

In an ideal longitudinal study of pregnancy all patients would have measurements at the same gestational age and at the same time intervals. Such a design permits within-subject comparisons using paired statistical tests, and meaningful results may be obtained with small numbers of subjects, but who have to undergo repeated measurements. In practice, patients may alter their appointments or miss them altogether, leading to incomplete data which are difficult to analyse. On the other hand, it may be easier to recruit a large number of subjects to undergo a single measurement in a cross-sectional study, but it is still difficult to get sufficient numbers at each gestational age, so a range of gestational ages has to be grouped together resulting in some loss of detail. Another problem is that the composition of each group may differ in respect of other factors than gestational age, such as maternal age.

In our study, patients were recruited over a wide range of gestational ages and were studied on a variable number of occasions at irregular intervals. However, the longitudinal design ensured that the composition of the group changed little from one gestational age to the next, and there were no major differences in maternal age structure at various gestational ages or between control and pregnant groups.

Time of increase of minute distance

We have shown that there is a statistically significant increase in minute distance of about 15% by 4 weeks gestation, just 2 weeks after conception, the increase more than doubling thereafter. These findings are consistent with those of Werko (1950), and Walters *et al* (1966) who found increases in cardiac output in patients between 7 and 12, and between 8 and 11 weeks gestation. More recently, Atkins *et al.* (1981), using impedance cardiography, showed a significant increase over the pre-pregnancy level at 12 weeks gestation.

Comparison of cardiac output in supine and left lateral positions

In our non-pregnant control subjects, stroke distance was 5·4% less in the left lateral than in the supine position, but the increased heart rate in the lateral position was almost fully compensatory and there was no significant difference in minute distance between the two positions. Ueland *et al.* (1969) reported stroke volume 2·5% less in the left lateral than in the supine position in 11 patients at 6–8 weeks postpartum. Atkins *et al.* (1981*b*) studied the rank order of stroke volume and cardiac output in six different positions in 19 non-pregnant subjects. Stroke volume was 6·6% less in the left lateral than in the supine position, but there was no significant difference in cardiac output. Using transcutaneous aortovelography, Newman *et al.* (1983) reported a reduction in cardiac output of 4·8% in the left lateral compared with the supine position, but did not comment on stroke volume or distance.

In early pregnancy it is to be expected that the same relative magnitude of stroke distance in the two positions would be maintained. At 40 weeks, supine stroke distance was 6% less than in the left lateral position but in the first postpartum week and at the 6 week postpartum visit the non-pregnant relativities had been restored. In the study reported by Atkins *et al.* (1981*a*) the transition occurred at 24 and 32 weeks in two groups of pregnant subjects, although at term the relative stroke volumes had reverted to the non-pregnant proportions in one group and values were 10·8% more in the left lateral position in the other group. Newman *et al.* (1983) found that cardiac output was increased by 0·18% in the left lateral compared with the supine position during the last 4 weeks of pregnancy.

These results are consistent with there being a modest obstruction to venous return in the supine position in late pregnancy, but because of a compensatory tachycardia the excess of minute distance in the left lateral position in our study was never more than 5%. This is difficult to reconcile with authors who report much greater differences between cardiac output in the supine and lateral positions in the last trimester, and the clinical observation that some patients have a marked fall in cardiac output in the supine position. Thus, Lees *et al.* (1967) found cardiac output to be 20% higher in the right lateral than in the supine position, and Vorys *et al.* (1961) and Ueland *et al.* (1969) reported increases of 14 and 27% in the left lateral compared with the supine position.

If a woman in late pregnancy lies supine in bed and restricts her venous return, she is likely to adjust her position and restore her cardiac output to normal. However, lying on an examination table during an invasive investigation, particularly where the objective of the study is to demonstrate the effect of posture, it is possible that she might be prevented or inhibited from moving, so that the fall of cardiac output would be progressive. In our study, adjustment of position during Doppler measurements was not seen, but had it occurred it would certainly have been noticed. Presumably, the short period of recumbency made significant venous obstruction unlikely.

The explanation for these discrepant results may also partly reside in the observation that in late pregnancy the sequence as well as the position in which the measurements are made may affect the value of minute distance (Rawles *et al.* 1987).

Cardiac output in the last trimester

It seems improbable that in studies performed before discovery of the supine effect strict attention would have been paid to maintenance of an undisturbed supine position throughout the period of investigation. Thus the fall in cardiac output in the third trimester described by Adams & Alexander (1958), Werko (1950), Palmer & Walker (1949), Hamilton (1949), Bader *et al.* (1955) and Walters *et al.* (1966) and other workers is most unlikely to be entirely attributable to the supine effect. These authors respectively describe increases of cardiac output of 32, 18, 39, 27, 40 and 26% at about 28, 18, 22, 28, 26 and 26 weeks gestation, and all report a subsequent decline to values at term ranging from 12% below to 24% above the non-pregnant normal. The absolute values of cardiac output obtained by some of these authors are unreliable because they used methods that are now obsolete, but there is less reason to doubt their ability to measure serial changes.

In three subsequent reports the authors were aware of the supine effect and made measurements of cardiac output in a lateral position. Ueland *et al.* (1969) showed a rise of 40% at 30 weeks falling to 14% at term. Pyörälä (1966) reported rises of 35% at 21 weeks and 38% at 28 weeks, sustained at 34% at 36 weeks; but closer inspection reveals that for each gestational period he gives a median value of cardiac output rather than the mean. Fortunately the raw data are published, and calculation of mean values gives somewhat different results with increases of 42, 28 and 27% at mean gestational ages of 21, 28 and 36 weeks respectively.

Lees *et al.* (1967) reported a serial study in five patients in the right lateral position with mean cardiac outputs of 6·10, 6·18 and 6·26 litre/min in the first, second and third trimesters. However, in a cross-sectional study described in the same paper, the respective figures were 5·79, 6·12 and 5·74 litre/min in 6, 3 and 9 subjects. Thus, the contention that there is no fall of cardiac output in the third trimester rests on the results from five subjects studied in the right lateral position.

Recently, using the combination of Doppler ultrasound and echocardiography, James *et al.* (1985) reported a rise in cardiac output of 36% at 25–28 weeks gestation, falling to about 5% at term, with no difference between supine and left tilt positions.

Spätling (personal communication) studied 20 patients in the left lateral position using an indirect Fick method to measure cardiac output. Compared with the 6–8 week postpartum value the maximum rise was of 37% at 28 weeks, falling to 22% at term.

Atkins *et al.* (1981*a*) reported maximum values of cardiac output in the left lateral position at 8–12 weeks gestation with a subsequent decline to less than the normal value. In a second series of patients, a maximum rise of 24% was again seen at 12 weeks with a subsequent fall to a value at term 6% below the pre-pregnancy value. However, doubts have been raised about the validity of impedance cardiography in longitudinal studies because of alterations in lung mechanics and the circulation during pregnancy (de Swiet & Talbert 1986).

Our results are thus fully consistent with previous published work. We found maximum increases of minute distance of 37% at 16 weeks in the supine position and 30·2% at 24 weeks in the left lateral position, and in both positions minute distance fell to non-pregnant control values at 40 weeks.

Acknowledgments

The patients in this study were under the care of Professor Arnold Klopper and we are indebted to him for his enthusiastic collaboration.

The results presented in this paper were analysed, and the paper drafted, in the Perinatal Physiology Laboratory of the Department of Obstetrics, University Hospital, Zürich, during a period of sabbatical leave granted to J.R. by the University of Aberdeen. We are greatly indebted to Professors Renate and Albert Huch for their generous hospitality and provision of research facilities and for many stimulating and helpful discussions.

F.M.Mc. was Research Fellow of the Association of Anaesthetists of Great Britain and Ireland at the time of the study.

We are grateful to Grampian Health Board for a research grant.

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Received 7 April 1986
Accepted 27 February 1987

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 507–511

The effect of position and delay on stroke and minute distance in late pregnancy

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Summary. Stroke and minute distance were measured in 12 women in late pregnancy using Doppler ultrasound. In each patient two sets of measurements were made every 2 min for 20 min in the supine and left lateral positions, the sequence of positions being reversed on the second occasion. Within each of the four 20 min measurement periods there were no significant changes with time in stroke distance, heart rate, or minute distance, or in their coefficients of variation. From this evidence there is no justification for delaying the measurement of cardiac output until a 'steady state' is reached. The measurements were influenced both by the sequence and the position in which they were taken, the effects being additive. Overall, stroke distance was 5·1% greater in the left lateral than in the supine position, heart rate was 3·7% less and minute distance not significantly different. Independent of posture, stroke distance was 6·5% greater in the second period of measurement than in the first, heart rate was 3% less and minute distance 2·8% more. In late pregnancy the relative magnitude of cardiac output in the left lateral and supine positions has to be interpreted in the light of a stepwise increase of aortic blood flow with change of posture.

In clinical studies, the measurement of cardiac output is usually performed after a time delay which is believed to be necessary to allow the circulation to adopt a 'steady state'. Although this practice is widespread there is little published evidence in its support, or to give guidance on the optimum time delay.

In the non-pregnant state and in early pregnancy cardiac output may be little different in the supine or left lateral positions, but in late pregnancy the gravid uterus may partially obstruct the inferior vena cava, reducing venous return and cardiac output particularly in the supine position. However, there are widely different estimates of the magnitude of this effect, which could result from differences in procedure. In particular, it is possible that the reduced cardiac output in the supine position could be a function of the time spent in that position before the measurement is made, a steady state never being attained.

We have therefore made repeated measurements of aortic blood flow in late pregnancy to determine the time necessary to reach a 'steady state', and to compare aortic flow in left lateral and supine positions measured after various time delays and in different sequence.

Patients and methods

Twelve women in the last trimester of singleton pregnancy were studied with their informed con-

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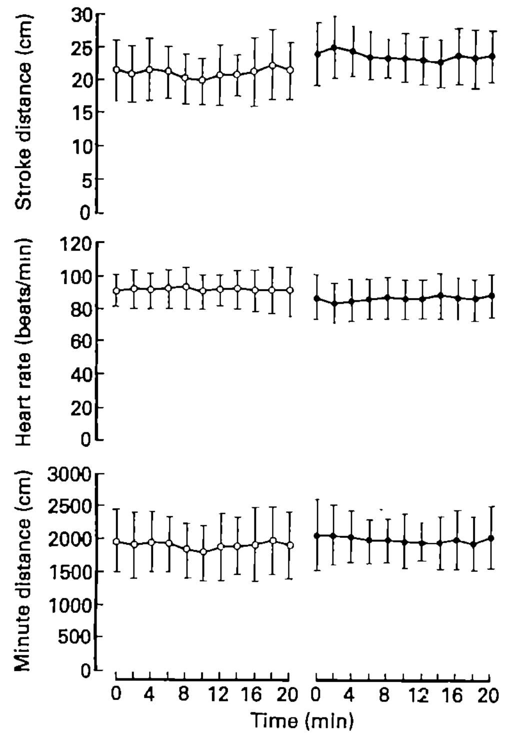

Fig. 1. Mean (±SD) stroke distance, heart rate and minute distance measured at 2-min intervals in 12 women in late pregnancy during 20 min in the supine position (○) followed by 20 min in the left lateral position (●).

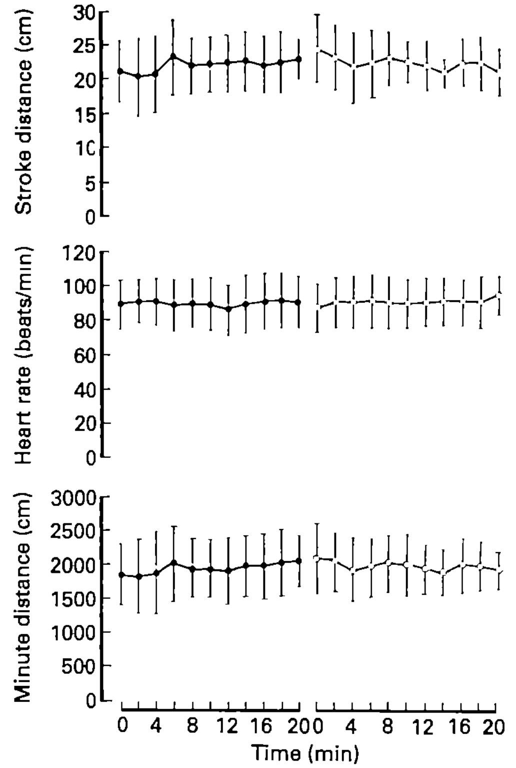

Fig. 2. Mean (±SD) stroke distance, heart rate and minute distance measured at 2-min intervals in 12 women in late pregnancy during 20 min in the left lateral position, (●) followed by 20 min in the supine position (○)

sent. Their mean age was 29 years, and their mean gestational age 35 weeks (range 33–40); none was in labour or taking tocolytic drugs. Immediately before the study patients were fully ambulant. The study was conducted in two 40-min parts with an interval of 5 min during which patients walked about freely and went to the toilet. Each part of the study consisted of 20 min in the left lateral and 20 min in the supine position, the order of positions being reversed in the second part of the study. The first six patients commenced the study in the supine and the next six in the left lateral position. Every 2 min during each of the four 20-min observation periods aortic blood flow was measured using Doppler ultrasound, as described previously (McLennan *et al.* 1987). From an average of 13 (SD 2·8, range 7–27) consecutive beats, the stroke distance, heart rate and minute distance were calculated on 11 occasions in each of the four observation periods, which represent all permutations of position and sequence. Paired *t*-tests and analysis of variance were used to evaluate the results.

Results

Effect of time

One-way analysis of variance in each observation period showed no significant change with time in the mean values of stroke distance, heart rate of minute distance (Figs 1 and 2). Neither was there a significant difference in the coefficients of variation of these measurements made in the first or second 10 min of each observation period. In subsequent analyses results in each period were therefore pooled and the mean values are shown in Fig. 3.

Effect of position and sequence of measurement

The results are given in Table 1. Overall, stroke distance was 5·1% greater in the left lateral than in the supine position ($P<0·001$), heart rate was

Table 1. Mean (SD) of stroke distance, heart rate and minute distance measured first or second in supine and left lateral positions. Eleven measurements were made at 2-min intervals in 12 patients. Mean differences (significance) by paired *t*-tests also shown

		Supine	Differences	Left lateral	Combined
			Latl-Supl		
Measured first	Stroke distance	20·8 (4·23)	1·0 ($P<0·05$)	21·8 (4·58)	21·3 (4·43)
	Heart rate	90·7 (11·3)	−2·0 ($P<0·05$)	88·7 (14·2)	89·7 (12·8)
	Minute distance	1890 (457)	27·0 (NS)	1916 (464)	1903 (460)
	n	132	d.f. = 131	132	264
Differences		Sup2-Supl		Lat2-Latl	2nd–1st
	Stroke distance	1·3 ($P<0·01$)		1·5 ($P<0·001$)	1·4 ($P<0·001$)
	Heart rate	−1·4 (NS)		−4·1 ($P<0·001$)	−2·7 ($P<0·001$)
	Minute distance	63·6 ($P<0·05$)		42·2 (NS)	52·9 ($P<0·001$)
	d.f.	131		131	263
			Lat2-Sup2		
Measured second	Stroke distance	22·1 (4·06)	1·2 ($P<0·01$)	23·3 (3·95)	22·7 (4·43)
	Heart rate	89·3 (13·7)	−4·7 ($P<0·001$)	84·6 (12·1)	87 0 (13·1)
	Minute distance	1953 (390)	5·6 (NS)	1959 (397)	1956 (393)
	n	132	d.f. = 131	132	264
			Lat-Sup		
Combined	Stroke distance	21·5 (4·19)	1·1 ($P<0·001$)	22·6 (4·33)	22 0 (4·29)
	Heart rate	90 0 (12·6)	−3·3 ($P<0·001$)	86·7 (13·3)	88·3 (13·0)
	Minute distance	1922 (426)	16·3 (NS)	1938 (431)	1929 (428)
	n	264	d.f = 263	264	528

3·7% less ($P<0·001$) and minute distance 0·9% more (NS). Independent of posture, stroke distance was 6·5% greater in the second period of measurement than in the first ($P<0·001$), heart rate was 3% less ($P<0·001$) and minute distance 2·8% more ($P<0·05$).

The summary result of a two way analysis of variance showing the effect of the sequence and position of measurement on stroke distance, heart rate and minute distance is given in Table 2. The effects of both sequence and position are independently highly significant for stroke

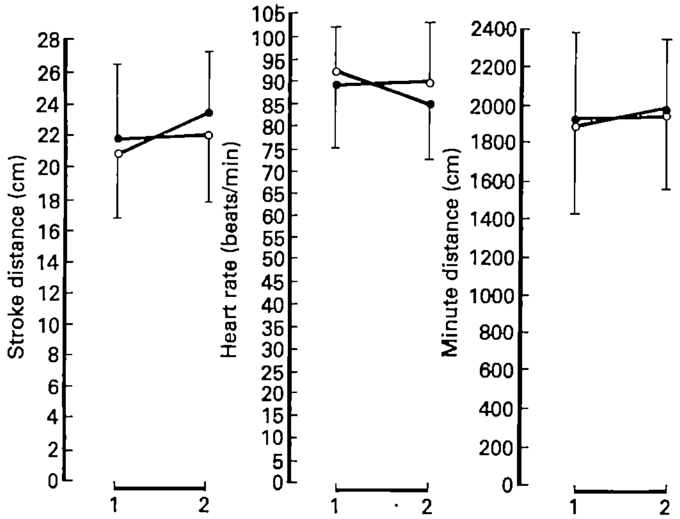

Fig. 3. Mean (±SD) of stroke distance, heart rate and minute distance in four measurement periods of 20 min, in supine (○) followed by left lateral (●) position, and left lateral (●) followed by supine (○) position.

Table 2. Summary of two-way analysis of variance to show the independent effect of sequence and position on stroke distance, heart rate and minute distance

		Variance ratio	*P*
Sequence	Stroke distance	14·23	<0·001
	Heart rate	5·95	<0·025
	Minute distance	2·02	NS
Position	Stroke distance	9·04	<0·005
	Heart rate	8·87	<0·005
	Minute distance	0·19	NS
Interaction	Stroke distance	0·03	NS
	Heart rate	1·40	NS
	Minute distance	0·08	NS

distance and heart rate though not for minute distance.

Discussion

In late pregnancy cardiac output is generally greater in the left lateral than in the supine position but it is clear from our results that the sequence of measurements, and probably also their timing, profoundly affects their relative values.

In each of the 20-min observation periods there was no significant change with time in the mean values of stroke distance, heart rate or minute distance, or their variability, measured as the coefficient of variation. On this evidence there is no justification for delaying the measurement of cardiac output until a 'steady state' is reached, vindicating the protocol of rapid measurement described previously (McLennan *et al.* 1987). Measurements at the end of a 20-min rest period are not significantly different from those at the beginning.

A surprising finding was that mean values of stroke distance and, to a lesser extent, minute distance were greater in the second observation period than in the first, regardless of the posture. This could be an artefact, for example, due to improved operator skill with repeated measurements, but that seems unlikely since the Doppler ultrasound technique we used is learned very quickly and the measurements were made by experienced operators. Also, the sequence of measurement has an effect of similar magnitude on heart rate, whose measurement is independent of operator skill. The effect of measurement sequence on stroke and minute distance is therefore likely to be a genuine phenomenon.

It seems probable that the magnitude of the increase of minute distance between the first and second observation periods is related to the length of time spent in the first position, though we did not directly test that hypothesis. When the measurements in either sequence were pooled, minute distance was 0·8% more in the left lateral than in the supine position. This corresponds to a value of 0·18% found by Newman *et al.* (1983) who eliminated the sequence effect by randomizing the order of positions. McLennan *et al.* (1987) found that at 40 weeks gestation, minute distance in the left lateral position was 3·9% more than in the supine position which had been maintained for about 3 min previously (McLennan *et al.* 1987). This compares with an excess of 3·6% in the left lateral position in this study after the first, supine posture was maintained for 20 min. The greatest postural differences in cardiac output reported, of 13% (Vorys *et al.* 1961) and 26% (Ueland *et al.* 1969) have been from studies using invasive techniques. Here the left lateral measurements were taken after an unspecified length of time spent in the supine position, required for the insertion of the catheters and the first measurement.

Our own results and the discrepant results in the literature may be explained as follows. The increase in minute distance seen with change of posture represents a stepwise manifestation of a trend to increase cardiac output while recumbent. This is unexpected since cardiac output is believed to increase by ambulation and fall with rest and recumbency. In late pregnancy, however, venous return may be markedly impeded in the upright posture (Schneider *et al.* 1984) giving rise to venous pooling and oedema of the legs (Hytten & Taggart 1967). While recumbent the fluid pool in the legs lessens progressively but blood only re-enters the circulation with each change of posture and operation of the muscle pump. This results in a stepwise increase in cardiac output, the size of each step dependent on the length of time spent in the position before the postural change. The return of the venous pool to the circulation is greater when changing from supine to left lateral position than the reverse because of partial obstruction of venous return in the supine position by the gravid uterus.

The hypothesis outlined above is capable of verification, but even if the explanation proposed is incorrect we have shown that in late pregnancy the relative magnitude of cardiac output in left lateral and supine positions has to be interpreted in the light of a stepwise increase of aortic blood flow with change of posture.

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Received 4 April 1986
Accepted 27 February 1987

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 512–517

A randomized control study of oxytocin augmentation of labour. 1. Obstetric outcome

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Summary. Sixty women who were progressing slowly in spontaneous labour were assigned at random to three management protocols. Group 1 were observed without the use of oxytocin for 8 h while groups 2 and 3 were managed with a low-dose and high-dose oxytocin protocol respectively. The caesarean section rates were not significantly different between the three groups: 45%, 35% and 26% respectively. Cervical dilatation rate increased significantly after oxytocin infusion in both treatment groups compared with controls. The 'delay-to-delivery' interval and second stage duration were significantly shorter in the high-dose group than in the control group. There were no measureable differences in the condition of the newborn infants between the three groups.

Variations of the 'active management of labour' described by O'Driscoll *et al.* (1969, 1970, 1973, 1977, 1984) and O'Driscoll & Meagher (1980) are widely used in managing slow progress in spontaneous primigravid labour in the belief that high-dose oxytocin infusion minimizes the need for caesarean section for dystocia (O'Driscoll *et al.* 1984). However, whereas O'Driscoll & Meagher (1980) achieved an intrapartum caesarean section rate of 1·2%, two non-controlled studies of 'active management' (Boyle *et al.* 1980; Cardozo *et al.* 1982) have reported intrapartum caesarean section rates of 8·6% and 8·7% respectively. There is a need for prospective studies before the benefits of active management can be completely accepted (Studd *et al.* 1982). To date no prospective randomized studies of oxytocin augmentation of spontaneous labour have been reported to confirm the value of high-dose oxytocin augmentation. In view of the known dangers of poorly controlled oxytocin infusion, and the fact that complications of its use now constitute a major cause of litigation in obstetrics (Fuchs 1985), we decided to carry out the pilot study reported here.

In an observational study of oxytocin augmentation of slow spontaneous labour using a low-dose oxytocin infusion regimen (Steer *et al.* 1985) it was found that the caesarean section rate following augmentation was 25%. We designed a prospective study to test the hypothesis that high-dose oxytocin infusion would reduce the need for caesarean section, in a group of women with slowly progressing labour, to under 20%, while a non-treatment group would require caesarean delivery and/or oxytocin in 80% or more cases.

Power calculations demonstrated that to have a 90% chance of confirming a difference between the high-dose oxytocin and control groups, significant at the 0·05 level (a = 0·05), the study would require 12 women in each treatment arm. A similarly significant difference between the low-dose oxytocin and control groups would require 19 in each group. In addition the study was also designed to detect differences of uterine activity which to achieve a 90% power (1−b = 10%) of detecting differences at a = 0·05 was expected to require groups of 30 in

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each arm. In fact differences were demonstrated at values of *n* much less than this. Our original plan was to recruit 50 women in each group, thus easily fulfilling the power requirements. However, this was not achieved due to limitations of time; 60 women were eventually recruited into the pilot study reported here and in Bidgood & Steer (1987).

Patients and methods

Women were eligible for the study if they were in their first spontaneous labour, with vertex presenting and within 3 weeks of term. All women were given an explanatory sheet at the antenatal clinic which summarized the study protocol and requested their consent in the event of slow progress in labour. The diagnosis of labour was established by: full effacement of the cervix and a dilatation of at least 3 cm, regular contractions requiring analgesia with a frequency of at least one every 5 min and partographic evidence of cervical progress. Spontaneous rupture of membranes with contractions but no evidence of progressive cervical dilatation was not considered sufficient evidence of labour for the purposes of the study. The women were identified by the labour ward staff as requiring augmentation if cervical dilatation was progressing at <0·5 cm/h. Any woman whose membranes were intact was first treated by artificial rupture of membranes (ARM) followed by a 4-h period to observe if augmentation of cervical dilatation resulted. The diagnosis of labour and delay was reviewed by K.A.B. in each woman before she was admitted to the study.

All eligible women who developed slow progress in labour were interviewed and each gave verbal consent before entry into the trial. Sixty women were recruited to the trial, 58 of them had elected to have epidural analgesia before they entered the study. Of the other two women, epidural analgesia was contraindicated in one by existing multiple sclerosis, and the second elected not to have epidural but subsequently demanded to be delivered by caesarean section in spite of progressive cervical dilatation.

On diagnosis of delay, an initial examination was performed by K.A.B. to document the cervical score and to insert a Sonicaid-Gaeltec intrauterine catheter to measure intrauterine pressure (IUP). All patients had continuous fetal heart rate (FHR) monitoring with either a fetal scalp electrode or an ultrasound transducer. Recordings were made on a Sonicaid FM3R fetal monitor. Active contraction area/15 min (uterine activity integral, UAI) was measured with the Sonicaid UAI module. At least 1 h of IUP measurements were taken as a control period. Recording was then continued until the start of active pushing in the second stage or until a decision to perform caesarean section had been taken. Intravenous glucose and electrolytes were given as clinically indicated. All clinical decisions were taken by the normal staff of the labour ward with K.A.B. as an observer.

During the control period random allocation to one of three management protocols was achieved by drawing consecutive sealed envelopes containing the instruction 'Control (group 1), or Automatic Infusion System (group 2) or High-Dose (group 3)' from 150 envelopes shuffled at the beginning of the study. After initiating uterine activity monitoring, K.A.B. left the labour ward to draw the allocating envelope, and hence initial observations were not available to bias allocation. It was theoretically possible for a patient entered into the trial to be delivered before randomization but this did not occur.

The three management protocols were as follows:

Group 1. Oxytocin was deferred for 8 h. At the end of this period oxytocin was given at the discretion of the supervising clinician.

Group 2. The automatic infusion system (AIS) was used according to the algorithm of Carter & Steer (1980) to detect those women whose uterine activity was below 700 kPas/15 min. In these women, oxytocin was infused at an initial rate of 2 mU/min and increased by 2 mU/min every 15 min until a stable phase of uterine activity was detected or UAI exceeded 1500 kPas/15 min, whereupon the infusion rate was halved to a maintenance level. Women with UAI levels of >700 kPas/15 min were not given oxytocin.

Group 3. Oxytocin infusion was started at 7 mU/min and increased by 7 mU/min every 15 min, limited by a frequency of 7 contractions in 15 min or by abnormality in the FHR trace.

Cervical dilatation was assessed by vaginal examination every 4 h. Hyperstimulation, defined as >7 contractions in 15 min and/or a rise in baseline tone of >1·33 kPa (10 mmHg) pressure, was noted. The decision to deliver by caesarean section was discussed with the consultant in charge of each patient, criteria for delivery being inadequate progress in the first or second stage of labour in spite of a uterine activity of >700 kPas/15 min for at least 8 h or maternal or fetal distress.

Fetal blood samples were obtained at entry to the study and again at full dilatation in those women who reached this stage. Umbilical cord artery and vein blood samples were taken at delivery before placental separation, into syringes containing dried heparin. pH, $P\text{CO}_2$ and $P\text{O}_2$ were measured with a Corning 178 pH/blood gas analyser, and lactate was estimated with Analox LM2 lactate analyser.

The study was approved by the St Mary's Hospital ethics committee.

Results

There was no significant difference between the study groups with respect to maternal stature, age and social class, and the gestational ages, birthweights and centile birthweights of the babies (Wilcoxon rank sum test). The patients did not show any difference from the overall primiparous population delivered at St Mary's Hospital during the study period.

The pattern of oxytocin administration was different in the three groups. Of the 20 women in group 1, only five received oxytocin at the end of the 8-h observation period, four received low-dose oxytocin via the AIS (three were delivered vaginally and one by caesarean section for failure to progress and one received high-dose oxytocin, she was later delivered by caesarean section for failure to progress. The mean infusion rate of oxytocin was 1·98 mU/min (range 0–18·5) and mean total dose was 0·52 units (range 0–3·89). There were no patients with hyperstimulation. Of the 15 women not given oxytocin, one requested caesarean section at the end of the 8-h observation period even though oxytocin was offered, and a second was delivered by section for FHR abnormality in the absence of fetal blood pH estimations, the decision being taken by the labour ward registrar in discussion with the consultant in charge. A further five women were delivered by caesarean section for failure to progress. Thus, 8 of the 20 women in this group were delivered vaginally without oxytocin (40%).

In group 2, 13 women received oxytocin during the treatment period while the remaining eight always had UAI levels >700 kPas/15 min. The mean infusion rate was 3·0 mU/min (range 0–16·82), with a mean total dose of 1·34 units (range 0–12·36). There were no patients with hyperstimulation. In this group one infusion was terminated manually in response to late decelerations on the trace; as there was also arrest of cervical dilatation a healthy infant was born by caesarean section.

In group 3 all women received oxytocin. The average infusion rate administered was 9·46 mU/min (range 0·28–28·9) and mean total dose was 2·43 units (range 0·11–9·98). Evidence of hyperstimulation was seen in seven patients within 15 min after the start of infusion at 7 mU/min. In three patients the hyperstimulation resolved after a further 15 min despite continuing oxytocin at the same rate. In three patients it did not resolve and the high-dose oxytocin regimen was rejected in favour of the AIS; the patients were classified as a high-dose regimen 'failures'. In one patient the hyperstimulation was associated with late decelerations which persisted after the infusion was terminated; fetal blood pH was 7·15 and she was delivered by caesarean section.

Both the numbers receiving oxytocin and the mean infusion rates used were significantly different between the three groups (Fisher's exact and Wilcoxon rank sum tests $P<0{\cdot}025$).

The modes of delivery by group are shown in Table 1. The caesarean section rates were lowest in the high-dose oxytocin group and highest in the non-treatment group. However, the differences did not reach statistical significance ($\chi^2 = 1{\cdot}6346$, d.f. = 2).

All the groups included women whose cervical dilatation rate increased during the experimental period, as well as others who showed no change or even slowing of cervical dilatation (Fig. 1). The high dose group had significantly more women who showed an increase in cervical dilatation rate than either of the other two groups (Wilcoxon rank sum test, $P<0{\cdot}05$ and $<0{\cdot}01$). The low dose and control groups were not significantly different, although a trend is seen.

Although the admission-to-delivery interval was not significantly different between the three groups (Wilcoxon rank sum test) there was a trend toward shorter labours in the high-dose group. When the delay-to-delivery interval and the duration of the second stage were compared between groups there was a significant shortening in the high-dose group compared with either

Table 1. Obstetric outcomes in each group

Variable	Control (*n* = 20)	AIS (*n* = 21)	High-dose (*n* = 19)
Mode of delivery *n* (%)			
Caesarean section	9 (45%)	7 (33·3%)	5 (26·3%)
Kjellands forceps	2 (10%)	5 (23·8%)	1 (5%)
Low forceps	6 (30%)	4 (19%)	7 (36%)
Spontaneous	3 (15%)	5 (23·8%)	6 (31·5%)
Hyperstimulation	0	0	7
Rate of cervical dilatation (cm/h)			
Before delay			
mean (SD)	0·233 (0·11)	0·225 (0·12)	0·182 (0·099)
range	0·08–0·5	0·06–0·25	0–0·4
At delay			
mean (SD)	4·9 (1·7)	5·3 (1·7)	4·6 (1·2)
range	3–8	3–9	3–7
After delay			
mean (SD)	0·408 (0·436)	0·535 (0·406)*	0·932 (0·685)*
range	0–1·5	0–1·75	0–2
Admission—delivery interval (h)			
mean (SD)	27 (8·1)	25 (6·7)	23 (7·8)
range	13–45	14–39	12–49
Delay—delivery interval (h)			
mean (SD)	11·1 (3·8)	11·3 (6·1)	7·8 (2·7)
range	4–18	4–34	3–14
Duration of second stage of labour (h)			
mean (SD)	2·45 (1·4)	3·6 (2·0)	2·07 (1·1)*
range	0–5	0–7	1–5
	(*n* = 11)	(*n* = 15)	(*n* = 14)

* Indicates the results which differ from the control group significantly at the 5% level or below

of the other groups ($P<0{\cdot}01$, Wilcoxon rank sum test, Table 1).

Neonatal outcome was not significantly different between the three groups (Table 2).

Discussion

The results support the null hypothesis that oxytocin does not reduce the caesarean section rate in this highly selected group. However, the numbers are small and the calculated confidence limits, −0·104 to 0·484 (Armitage 1971) make it impossible to confirm a difference when the caesarean section rate in the control group is less than 48%, even if high-dose oxytocin enabled caesarean section to be avoided entirely (an unlikely hypothesis). We anticipated that most of the women in the control group would need oxytocin if they were to avoid a caesarean section; however, even when oxytocin was not used, as in 15 of the 20 women in group 1 (controls), more than 50% achieved a vaginal delivery. The results are compatible with the hypothesis that oxytocin infusion can avoid the need for caesarean section in one in five slow labours, but a randomized prospective study of at least 320 labours (i.e. 158 in each group) would be needed to confirm or refute this at the 0·05 probability level (Lachin 1981).

As the study was not 'blind' and a placebo was not used in the control group, bias was possible in relation to allocation and management. However, uterine activity was very similar in the three groups at the time of randomization, as was cervical dilatation suggesting that allocation was truly random. Bias in management was minimized by having the experimenter isolated from clinical decisions. The longer second stages tolerated in the low-dose group may reflect bias in favour of the 'familiar' management protocol, as this was the standard method of augmentation used in the unit, but similar differences were not seen between the control and high-dose groups. The strict selection criteria ensured that only women with true slow labour were studied, with-

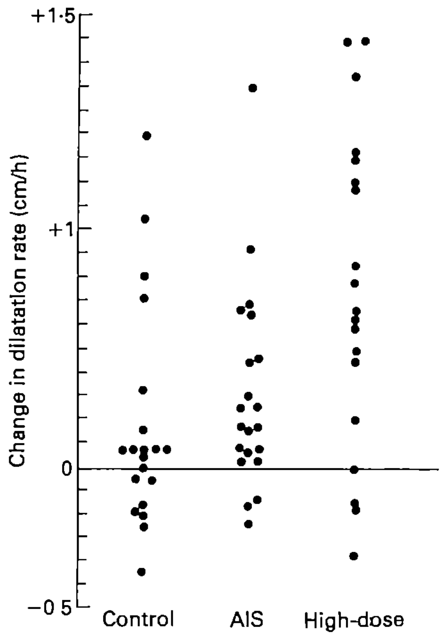

Fig. 1. The change in rate of cervical dilatation after observation or treatment in accordance with the randomization. Wilcoxon rank sum test: control *vs* AIS P = NS; control *vs* high-dose $P<0{\cdot}01$, AIS *vs* high-dose $P<0{\cdot}05$.

out dilution of the study group by over diagnosis of abnormality.

The overall intrapartum caesarean section rate in our unit during the study period was 8·9% (1984 Perinatal Statistics, NW Thames Region Obstetric Computer project). This was achieved with an augmentation rate in spontaneous primigravid labour of approximately 5%. In contrast, Boyle *et al.* (1980) and Cardozo *et al.* (1982) describe augmentation rates in excess of 40% and yet still had intrapartum caesarean section rates of 8·6% and 8·7% respectively. These results and those of the present study do not support the wholesale use of oxytocin if the objective is to avoid caesarean section.

Nonetheless, the use of high-dose oxytocin infusion appears to shorten labour by producing an increase in the rate of cervical dilatation and reducing the length of second stage. The low-dose regimen based on the AIS, although associated with a significant increase in the rate of cervical dilatation, did not reduce the delay-to-delivery interval because the second stage was longer than in the control group. This prolongation of the second stage may be a reflection of inadequate oxytocin in the second stage as a result of a reduced Ferguson reflex in the presence of epidural analgesia (Goodfellow *et al.* 1983). The effect of oxytocin was particularly evident in those women who developed arrest of

Table 2. Neonatal outcome by group assigned

	Group 1 (control)	Group 2 (AIS)	Group 3 (high-dose)
Umbilical blood	mean (SD) range	mean (SD) range	mean (SD) range
pH			
artery	7·27 (0·07) 7·16/7·42	7·27 (0·11) 6·9/7·4	7 27 (0·08) 7·02/7 38
vein	7·33 (0·06) 7·19/7·41	7·33 (0·07) 7·14/7·45	7·35 (0·07) 7·1/7·44
$P\text{CO}_2$(kPa)			
artery	53 (7·7) 40/68	54 (16) 28/103	51 (11·5) 34/90
vein	43 (8·9) 29/60	42 (8·7) 22/63	39 (9·7) 24/74
$P\text{O}_2$ (kPa)			
artery	17 (6·24) 8/31	18 (5) 11/30	18 (6) 8/32
vein	28 (7·9) 12/44	30 (4·2) 20/37	29 (8·9) 18/53
Base excess (mmol/l)			
artery	−3·4 (3·88) 3·5/−9·9	−3·7 (4) 1·7/−16·8	−4·3 (2·9) 0·9/−10·6
vein	−3·3 (3) 1·6/−8·5	−3·2 (2·6) 1/−9·3	−3·8 (2·2) 0·1/−9 1
Lactate (mmol/l)			
artery	3·07 (1·53) 0·75/6·9	3·7 (2·6) 1·7/12·6	3·6 (1·4) 0·4/6·7
vein	2·4 (1·1) 1/5	2·8 (1·4) 1·4/7·3	3·1 (1·4) 0·5/6·1
No. with Apgar score			
<7 at 1 min	5	6	2
<7 at 5 min	1	1	

the active phase, while those who continued to progress at the same slow rate throughout labour (primary dysfunctional labour) were less influenced by the use of either low- or high-dose rates of oxytocin. This observation is in accordance with Friedman (1978). However, we also demonstrated that the dosage of oxytocin needed to achieve these results produced hyperstimulation in 7 (37%) in the high-dose group. In three women this was sufficiently severe to require withdrawal from the study protocol and in a fourth patient hyperstimulation was associated with persistent late decelerations and she was delivered by caesarean section. This suggests that there may be hazards to high-dose oxytocin which are not justified by its effect on labour progress. Hyperstimulation occurred despite the fact that in no patient reached a dose rate of 40 mU/min with the manual regimen as invariably a contraction frequency of 7 in 15 was reached before to this dosage. This is contrary to the experience of O'Driscoll *et al.* (personal communication) who find that most of their patients will tolerate high doses of oxytocin. The reason for this discrepancy remains unclear. However, the observation that hyperstimulation may occur when initial infusion rates of around 8 mU/min are used is in keeping with the findings of Poseiro & Noriega-Guerra (1961).

We conclude that this small randomized study of a group of women in slow labour does not support the claims made on the basis of non-randomized trials and highlights the need for properly constructed studies.

Acknowledgments

We would like to thank all the midwives and junior medical staff who identified the study group and the consultants of St Mary's who allowed us to study their patients. Support for the study was provided by 'Action Research for the Crippled Child'.

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Received 13 March 1986
Accepted 7 October 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 518–522

A randomized control study of oxytocin augmentation of labour. 2. Uterine activity

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Summary. Uterine activity was measured in 60 women whose first labour was progressing slowly in the active phase. The mean level of active contraction area (uterine activity integral, UAI) before oxytocin augmentation was 898 (SD 458) kPas/15 min. UAI increased significantly with time, even in women not given oxytocin. UAI increased logarithmically with increasing oxytocin infusion rate. Levels of uterine activity before and after oxytocin infusion are correlated positively such that the higher the initial level of UAI the higher the UAI in response to oxytocin. However, the regression line approaches the line of identity such that even with high doses of oxytocin UAI would not be likely to exceed 2500 kPas/15 min. There is a positive correlation between uterine activity and cervical dilatation rate in unstimulated labour; however, this is less evident following oxytocin infusion. Increases in uterine activity below 1200 kPas/15 min result from both higher frequency and active pressure, whereas above 1200 kPas/15 min any increase is due mainly to a rise in frequency.

Although failure to make progress in labour is a common indication for caesarean section and oxytocin is widely used in the management of slow labours (Boyle *et al.* 1980; Cardozo *et al.* 1982; O'Driscoll *et al.* 1984), there are few published data on levels of uterine activity in slow labour. Such as exist refer exclusively to low dose oxytocin regimens with some form of feedback control from intrauterine pressure measurements (Seitchik & Castillo 1982; Steer *et al.* 1985). There are no accounts of the spontaneous evolution of uterine activity in slow labour, nor are there reports of the effects of high-dose oxytocin infusion.

As part of a pilot study of three regimens for the management of slow labour (Bidgood & Steer 1987) we studied the following. (1) The spontaneous level of uterine activity in untreated slow labour, and its evolution with time. (2) The effect of oxytocin in varying dosage. (3) The correlation of uterine activity with rate of cervical dilatation. (4) The contribution of the individual components (frequency, active pressure) to overall levels of uterine activity as measured by active contraction area (UAI).

Patients and methods

The study patients, selection, random allocation, methods of measurement and treatment protocol have been described in the preceding paper (Bidgood & Steer 1987).

In summary, 60 women were allocated at random to three protocols for management of slowly progressing first labour. Uterine activity was measured using a Gaeltec intrauterine catheter recording onto a Sonicaid FM3R monitor. In the first group the evolution of spontaneous uterine activity was observed for 8 h. In the second group an automatic infusion system

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(AIS) was used which gave oxytocin only to women with UAI levels <700 kPas/15 min, while in the third group a manually controlled high-dose oxytocin infusion regimen was used in all women.

Statistical analysis

To compare the evolution of uterine activity in labours of varying lengths, the test period has been divided into quarters by time, and the uterine activity per 15 min averaged over each of these quarters.

To avoid assumptions about the nature of UAI distribution, the significance of differences was tested using the Wilcoxon rank sum test. Data from all cases were pooled for the analysis of uterine activity and oxytocin dose rate. Since the uterine response to oxytocin infusion is known to be related geometrically to the dose rate (Caldeyro-Barcia *et al.* 1957; Turnbull & Anderson 1968) its logarithm has been used in comparison between dose rate and resulting UAI.

A computer file was made of UAI, mean active pressure and frequency of contractions, for each 15-min period. A total of 1787 measurement periods from 60 labours were processed using the 'SAS GRAPH' package (SAS Software Ltd.) on the University of London Computer Centre Amdahl 470V/8 system to produce Fig. 3.

Results

The levels of uterine activity are shown in Table 1. UAI in the control period was not significantly different between the three groups. Where no oxytocin was given during the 8-h study period (control group), there was a spontaneous increase in uterine activity which by the fourth quarter of labour was significantly greater than the control value ($P<0{\cdot}05$, Wilcoxon rank sum test). When low dose oxytocin was given, the increase in uterine activity was greater and more rapid but the levels of UAI were not significantly different from those in the control group in any quarter of the labour. High-dose oxytocin produced a rapid rise in UAI, with levels achieved in the first quarter of the study period higher than the levels ultimately reached in the other two groups. The levels were significantly higher in all quarters of labour ($P<0{\cdot}025$ or higher, Wilcoxon rank sum test).

In the control group there was an increase in uterine activity with time in 12 women (60%), no change in 2 (5%) and a decrease in 6 (30%) (Fig. 1a). However, the rise was greatest in those women whose initial level of UAI was low and least when the initial level was high such that the regression line approaches the line of identity at 2000 kPas/15 min. Therefore on average no increase would be expected in women with UAI already at or above 2000 kPas/15 min.

With low dose oxytocin (Fig. 1b) there was an increase in UAI in 16 women (76%) and no change in 4 (10%) while in one UAI decreased. The intercept of regression line with the line of identity suggests that on average there would be no increase with an initial UAI above 1800 kPas/15 min.

In the high-dose group 17 women (89%) showed an increase while 2 (11%) showed no change. The regression line still approaches the line of identity, suggesting that there would be no average increase in UAI with initial levels above 2500 kPas/15 min (Fig. 1c).

There was a correlation between the mean

Table 1. Uterine activity (UAI) in kPas/15 min by group and quarters of labour

	Group 1 (control) ($n = 20$)		Group 2 (AIS) ($n = 21$)		Group 3 (high dose) ($n = 19$)	
Time period	Mean	(SD)	Mean	(SD)	Mean	(SD)
Control	947	(489)	848	(440)	900	(463)
Quarter 1	1038	(460)	1069*	(494)	1529*	(515)
Quarter 2	1074	(474)	1100*	(485)	1758*	(594)
Quarter 3	1245	(583)	1321*	(440)	1733*	(579)
Quarter 4	1291*	(621)	1344*	(452)	1770*	(131)

* Indicates those values which are significantly different from the control level, using Wilcoxon's rank sum test; $P<0{\cdot}05$

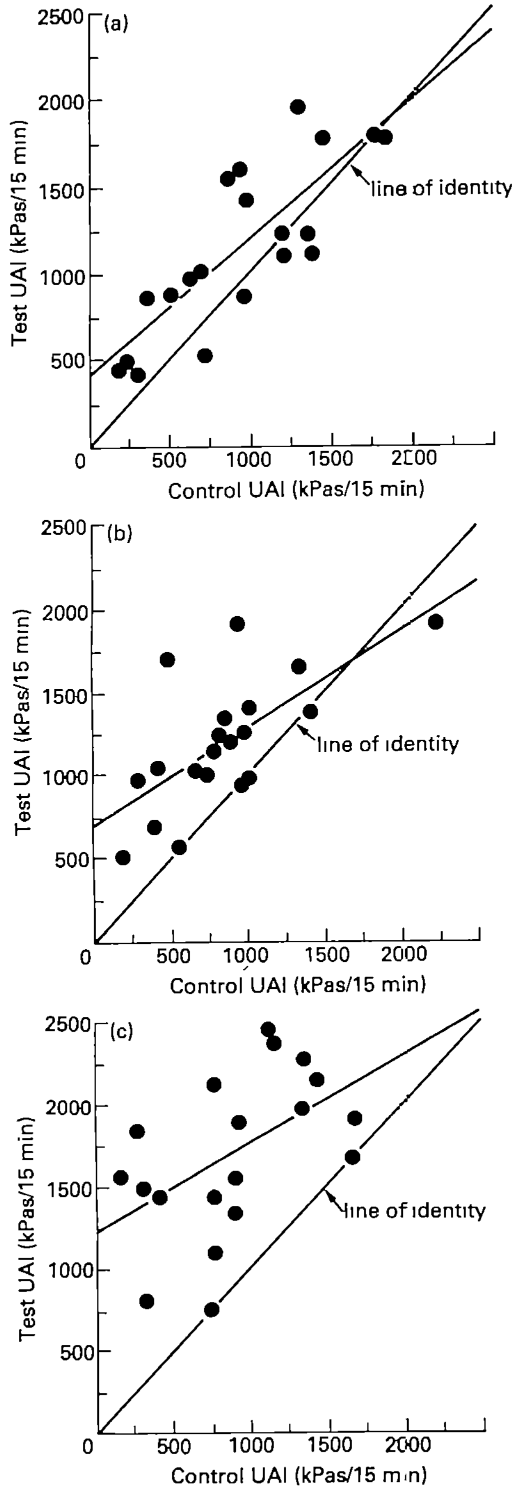

Fig. 1. The mean test UAI by initial UAI, subdivided by group. (a) Group 1: $n = 20$; $r = 0{\cdot}814$; $P<0{\cdot}001$. (b) Group 2: $n = 21$; $r = 0{\cdot}671$; $P<0{\cdot}001$ (c) Group 3: $n = 19$; $r = 0{\cdot}515$; $P<0{\cdot}001$.

UAI and the rate of cervical dilatation in the test period which was highest in the non-treatment group ($r = 0{\cdot}552$, $P<0{\cdot}001$), intermediate in the low-dose group ($r = 0{\cdot}401$, $P<0{\cdot}01$) and lowest in the high-dose group ($r = 0{\cdot}268$, $P<0{\cdot}05$).

Analysis of pooled data

In those women given oxytocin, there was a positive correlation between the logarithm of the dose rate and mean UAI increase ($r = 0{\cdot}448$, $P<0{\cdot}05$). The mean increase in UAI over whole labours is shown by geometrically increasing dose rate groups in Fig. 2.

Figure 3 shows the relation of frequency and active pressure with UAI with best fit line and 95% confidence limits. The change in UAI from 0 to 800 kPas/15 min is due mainly to an increase in active pressure; between 800 and 1200 kPas/15 min the increase is due equally to active pressure and frequency, while above 1200 kPas/15 min any increase in UAI results mainly from increased frequency.

Discussion

The results of this study confirm that slow labour is associated with low uterine activity. The mean level of UAI in the control period was 898 kPas/15 min. This is substantially lower than values previously reported for 'normal' labour: mean 1099 kPas/15 min (Steer *et al.* 1984); median at 5 cm 1269 kPas/15 min (Gibb *et al.* 1984) and median 1803 kPas/15 min (Cowan *et al.* 1982). However, it is significantly higher than the mean UAI reported for slow labour by Steer *et al.* (1985) (593 kPas/15 min, $t = 3{\cdot}36$, $P<0{\cdot}005$). As there is a spontaneous rise in UAI with time, shown in our control group, this difference may be a reflection of the relatively long period from labour ward admission to diagnosis of delay in this study (mean 15 h).

The rise in UAI in response to oxytocin was dose related. The rate of increase and mean level achieved was highest in group 3 and intermediate in group 2. The significant spontaneous increase (215 kPas/15 min) in uterine activity seen in controls suggests that the net response to oxytocin should be derived from this baseline. On this basis oxytocin has negligible effect until a dose rate of 2–4 mU/min is reached (Fig. 2) although Seitchik *et al.* (1984) suggest that the response would be greater if the dose rate were maintained for longer (up to 60 min). Thereafter

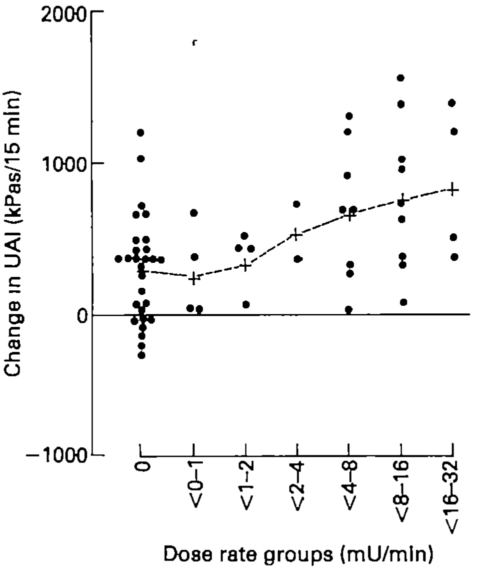

Fig. 2. The change in UAI with increasing oxytocin infusion rate.

the dose-response relation is logarithmic, such that 70% of the maximum response can be achieved with a dosage of 4–8 mU/min. This is compatible with the findings of Seitchik & Castillo (1983), who conclude that 4 mU/min is usually sufficient to augment hypocontractile labour. However, the greatest net response was seen with dose rates of 16–32 mU/min (576 kPas/15 min).

Steer *et al.* (1985) reported an inverse dose-response relation for oxytocin and UAI, while in the present study the relation was found to be direct. In the first study the dose was chosen by response, hence low doses were used when a sensitive uterus responded with a large increase in UAI, whereas high doses were only used in an attempt to produce a response from an insensitive uterus. In this study the positive correlation results entirely from the high-dose group where oxytocin was given regardless of response (unless hyperstimulation resulted). The range of response within dose groups is much larger than the differences between dose groups, which supports the hypothesis that the sensitivity of the uterus is the most important factor in the response to oxytocin stimulation (Beazley *et al.* 1975).

In all groups, the potential for increasing UAI was related to its initial level, the dose response being less the higher the initial UAI. This is in keeping with the findings of previous studies (Steer *et al.* 1975, 1985; Steer 1977). The correlation between UAI and the cervical dilatation rate is highest in the non-treatment group and lowest in the high-dose group. This is presumably because low uterine activity was a factor in the causation of slow progress in the non-treatment and low-dose groups whereas once uterine activity had been augmented maximally in the high-dose group only 'resistance to progress' remains to determine the rate of cervical dilatation.

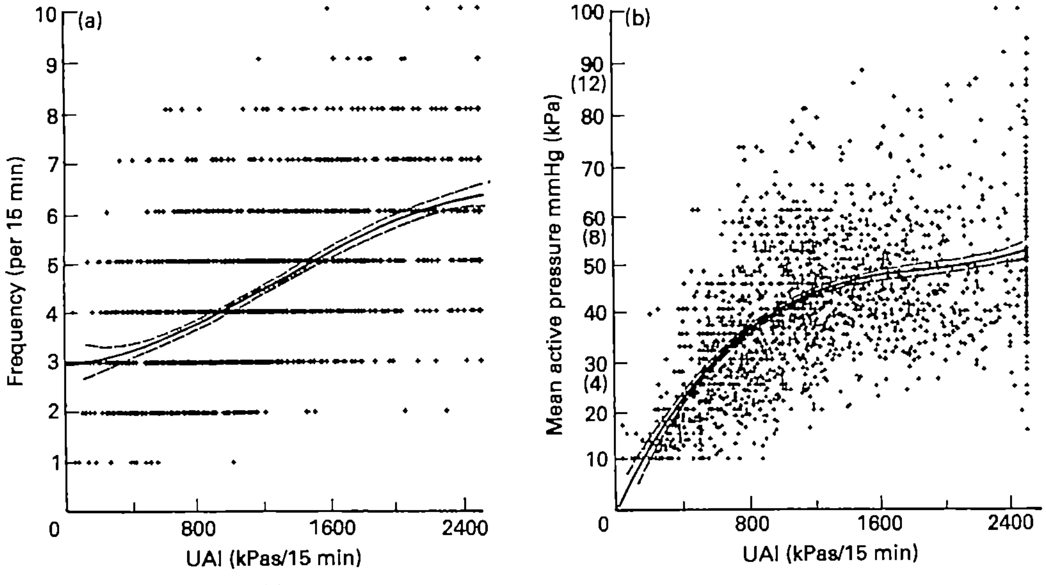

Fig. 3. The relation between (a) UAI and contraction frequency and (b) UAI and mean active pressure.

When the components of uterine activity were studied, we found that up to 1200 kPas/min, which is the mean value for normal spontaneous labour (Steer *et al.* 1984), increase in UAI is due to an increase in both frequency and active pressure. Further increase in UAI is associated with little increase in active pressure but a further doubling of frequency. This increase in frequency means a reduction in the recovery time for fetal oxygenation between contractions. Hence, since rate of cervical dilatation is associated mainly with active pressure rather than frequency (Caldeyro-Barcia & Reynolds 1950; Steer *et al.* 1984), it seems likely that stimulating UAI above 1200 kPas/15 min will produce only a modest increase in the rate of progress in labour while the risk of fetal hypoxia may be increased (Gordon 1984). This conclusion will be examined further in a subsequent paper.

Acknowledgments

We would like to thank all the midwives and junior medical staff who identified the study group and the consultants of St Mary's Hospital who allowed us to study their patients. Support for the study was provided by 'Action Research for the Crippled Child'.

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Received 13 March 1986
Accepted 12 November 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp 523–527

Maternal perception of sound-provoked fetal movements as a measure of fetal well-being

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Summary. Maternal perception of sound-provoked fetal movements was studied on 613 occasions in 259 risk pregnancies. The response was compared with a non-stress (N-S) test performed immediately after the sound stimulation. A positive response to sound stimulation, recorded as a fetal movement by the mother, occurred on 534 occasions (87%) and was always accompanied by a normal N-S test; sensitivity 100%. An inconclusive (3%) or negative response to sound (10%) had a specificity of 89% and a predictive value for a pathological N-S test of 19%. There was a positive correlation between inconclusive or negative test results and fetal growth retardation ($P<0{\cdot}01$), fetal hypoxia ($P<0{\cdot}05$) and neonatal mortality ($P<0{\cdot}05$). This rapid test may have a place as a simple first-line screening test.

Fetal ability to respond to sound vibration has long been recognized. In a systematic study of pregnant women at term, Paiper (1925) reported an increase in fetal movements immediately after sound stimulation, and Forbes & Forbes (1927) described a woman who experienced fetal movements whenever the audience applauded at a musical concert. Since then, there have been reports of fetal heart rate increase with sound stimulation (Sontag & Wallace 1936; Johansson *et al.* 1964; Grimwade *et al.* 1971) and it has been suggested that this acceleration in fetal heart rate could be used clinically in antepartum fetal monitoring (Goodlin & Schmidt 1972).

Recently sound stimulation of the fetus has gained considerable attention, especially in the United States, where the use of a fetal acoustic stimulation test (the FAS-test) has been described. It has been claimed that acoustic or, more accurately, vibro-acoustic stimulation of the fetus reduces the frequency of equivocal non-stress (N-S) tests (Trudinger & Boylan 1980; Serafini *et al.* 1984; Ohel *et al.* 1986), limits the need for oxytocin challenge tests (Read & Miller 1977) and reduces the duration of N-S tests (Davey *et al.* 1984; Smith *et al.* 1985).

Ultrasound studies (Gelman *et al.* 1982, Birnholz & Benacerraf 1983; Divon *et al.* 1985) have suggested that the fetal response to sound stimulation is analogous to the newborn startle reflex and that it is a consistent phenomenon from the 28th week of pregnancy. The startle reaction includes blink response, head aversion, arm movements and leg extension and is mostly felt by the mother as a pronounced fetal kick or movement. The present study is a preliminary report on a method of assessing maternal perception of this fetal startle reflex. The sound-provoked fetal movement (FM) is compared with the N-S test and with fetal outcome.

Subjects and methods

Maternal perception of sound-provoked FM was studied in 259 patients at the Department of Obstetrics and Gynecology, Danderyds Hos-

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pital, Karolinska Institutet in Stockholm, between June 1985 and January 1986.

All patients were recruited from the local high risk ward which is the largest delivery ward in the Stockholm area; 42% were treated as in-patients and the remainder were regular attenders at our high risk out-patient clinic. All patients volunteered for the study and gave informed consent. The risk factors in these 259 pregnancies are shown in Table 1. All patients knew that they were supposed to feel fetal movements at stimulation.

The sound stimulation test was always performed immediately before a conventional N-S test which was part of the routine surveillance in these patients. The N-S test was repeated at varying intervals in different patients depending on clinical circumstances.

Sound stimulation

The test procedure was as follows. The woman was placed in semirecumbent position. The sound stimulation was then given for 1–2 s with a hand-held battery-powered vibro-acoustic noise search (SERVOX). The 22 mm circular disc contact surface was applied firmly to the maternal abdomen directly overlying the fetal thorax. The noise search gives an approximate 110 dB intensity as measured in air 10 cm from the disc surface with a broad spectral peak at about 100 Hz. During sound stimulation the woman was asked if she felt fetal movements. A kick immediately following the sound stimulation was considered a positive response. If the patient did not feel any movements within 5 s, the stimulation was repeated twice within 30 s. If no FM were experienced during the three stimulations the test was considered negative or non-responsive (an abnormal test). If the patient was 'not sure', the test was classified as inconclusive. The test result was tabulated before the N-S test was performed.

Table 1. Principal risk factors in 259 high-risk pregnancies included in the study

Principal risk factor	No of patients
Suspected growth retardation	72
Pre-eclampsia or hypertension	46
Reduced fetal movements	22
Preterm contractions	22
Postmaturity	21
Antepartum haemorrhage	19
Diabetes mellitus	10
Twins	7
Others	40
Total	259

The N-S test was performed immediately after the sound stimulation with a Hewlett-Packard 8040 unit. The fetal heart tracing was assessed without any knowledge of the outcome of the sound stimulation test. A pathological N-S test was diagnosed as a non-reactive tracing with decelerations (Keegan & Paul 1980).

Statistical analysis

The sensitivity (proportion of pathological N-S tests selected by negative tests), specificity (proportion of normal N-S tests selected by positive tests) and predictive value (proportion of negative tests associated with pathological N-S tests) were calculated. The outcome in patients with positive tests was compared with that in patients with negative and inconclusive responses by the χ^2 test using Yates' correction for significance. *P*-values above 0·05 were not regarded as significant.

Results

Sound stimulation and N-S tests were performed on 613 occasions in 259 patients and sound-provoked FM were recorded on 534 (87%). On 64 occasions (10%) the response to sound stimulation was negative and 15 were graded as inconclusive (3%). Table 2 shows the results of the sound stimulation tests compared with the N-S tests. A positive test, i.e. the patient felt FM at sound stimulation, was always accompanied by a normal N-S test giving a sensitivity of 100%. An inconclusive or a negative test had a specificity of 89% and a positive predictive value of 19%. To avoid dependent multiple observations in the same patient, the result of the first test in each patient was compared with the corresponding N-S test (Table 3). The specificity and the positive predictive value of an inconclusive or negative test were in the same range as the values for the total sample (96% and 18% respectively).

Table 4 compares the pregnancy outcomes in the patients with positive and inconclusive or negative stimulation tests. Patients with both positive and negative or inconclusive test were referred to the inconclusive/negative group.

Table 2. Results of 613 paired sound-provoked fetal movement (SPFM) tests and non-stress (N-S) tests

Result of SPFM test	*n*	Result of N-S test: Normal	Result of N-S test: Pathological
Positive	534	534	0
Inconclusive	15	15	0
Negative	64	49	15

Table 3. Results of the first sound-provoked fetal movement (SPFM) test and the non-stress (N-S) test

Result of SPFM test	*n*	Result of N-S test: Normal	Result of N-S test: Pathological
Positive	248	248	0
Inconclusive	4	4	0
Negative	7	5	2

There was a positive correlation between inconclusive or negative tests and fetal growth retardation, hypoxia and mortality.

The infant in the positive group that died had a pronounced tracheal stenosis and the mother had suffered from a severe polyhydramniosis. All the three infants who died in the inconclusive or negative group were growth-retarded, two were associated with maternal hypertension and one with maternal heart failure.

More than two stimulations were performed in 30% of the patients and 7% had experienced more than five tests. The skew distribution in respect to the number of tests represents varying degrees of need for fetal surveillance. The possible significance of differences in response in the same fetus at different times was analysed in the 19 patients who had undergone more than five stimulation tests (Fig. 1). Of these patients, 11 (58%) had exhibited negative or inconclusive response on at least one occasion. The positive predictive value of a negative or inconclusive test was 13% in these patients, slightly lower than that in the total sample (19%).

Discussion

It is possible that, unlike healthy fetuses, compromised fetuses might not react with startle movements to external vibro-acoustic stimulation. If that is so, then a positive response to sound stimulation could obviate the need for an N-S test. The present study supports this suggestion since no Type II errors occurred (i.e., a positive response to sound stimulation was always followed by a normal N-S test). However, the number of patients with an abnormal N-S test was too limited to permit such a far reaching conclusion. Another explanation for the poorer outcome in the group of patients with an inconclusive or negative test could be that the most severe cases in the present study had experienced more tests and thereby increased their chance for a negative or inconclusive test result. In addition, with our protocol it was impossible to exclude a possible placebo effect since the vibro-acoustic stimulation was always perceived by the patient. Another matter of concern is fetal habituation to vibro-acoustic stimulation. Leader *et al.* (1982) have demonstrated a steadily diminished response when the same vibrotactile stimulus was presented repeatedly during the last 10 days of pregnancy. The authors suggest that the habituation represents learning. In the present study such a phenomenon was not observed. These questions need further clarification, and we will therefore continue to use

Table 4. Fetal outcome by result of the sound-provoked fetal movement (SPFM) test

Fetal outcome	Result of SPFM test: Positive (*n* = 206)	Result of SPFM test: Negative of inconclusive (*n* = 53)	Significance of difference (*P*)
Intrauterine growth retardation*	4	7	<0·01
Small-for-gestation†	–	5	<0·01
Hypoxia (Apgar score <7 at 1 min)	2	4	<0·05
Mortality	1	3	<0·05

* Diagnosed by repeated ultrasound screening, under the 10th centile or no significant growth within 2 weeks
† >SD below the mean birthweight according to the Swedish national curve.

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Fig. 1 Maternal perception of sound-provoked fetal movements in 19 patients who all had more than five tests. Positive response (□), negative response (■) and inconclusive results (▲) are given in consecutive order for each patient. Boxed squares represent patients with pathological non-stress tests

sound-provoked FM and N-S tests in the surveillance of pregnancies at risk.

Maternal subjective registration of spontaneous fetal movements is useful in the assessment of fetal well-being. However, long registration periods which cover changes in fetal activity state are required and great individual variability exists (Sadovsky *et al.* 1979, 1983). These disadvantages limit the usefulness of this method in the routine surveillance of normal pregnancies. It remains to be established if sound-provoked FM may overcome these disadvantages, but it is tempting to suggest that the method is less dependent on fetal state. The present study indicates that the same fetus may respond to sound differently on different occasions (Fig. 1). One may speculate that such cases may represent fetal compromise not detected by N-S tests and that sound-provoked FM is a more sensitive method. Reports by Myers (1977) that the first area in the fetal monkey brain to be affected by hypoxia is the auditory area add support to this suggestion.

The 110 dB intensity at about 100 Hz of the noise search used in the present study exceeds the background noise *in utero*, which has been estimated to be in the range of 75 dB (Walker *et al.* 1971; Vince *et al.* 1982; Baldwin *et al.* 1983). Studies of attenuation of sound through maternal tissues and uterine walls reveal an increasing attenuation with increasing frequency (Johansson *et al.* 1964; Bench 1968). With a frequency of 100 Hz it is reasonable to assume that the sound intensity will be only slightly muffled and probably no change in spectral composition will occur (Birnholz & Benacerraf 1983). In accordance with other authors we found that the stimulation at this frequency led to a marked fetal response (Leader *et al.* 1982, Birnholz & Benacerraf 1983). The stimulation is probably mediated through both the auditory and vestibular systems. The marked response may illustrate the effect of vibratory stimulation in a sensory deprived fetus, since it is believed that the fetus due to its relative weightlessness experiences a diminished perceptive input.

Finally, in a climate of increasing hospital costs there is an obvious need for less complicated, less expensive and less time-consuming methods for surveillance of fetal well-being. With easily applicable methods the fundamental problem in obstetrics concerning the critical selection of whom to test will be overcome. Maternal perception of sound-provoked FM may fulfill these requirements and might be useful as a simple first line screening test. Further studies to assess the prevalence of negative responses to sound stimulation in normal pregnancies and the prognostic efficacy of sound-provoked FM are in progress.

Acknowledgment

The studies were performed in co-operation with Siemens-Elema Ltd, Stockholm, Sweden.

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Received 10 April 1986
Accepted 23 October 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp 528–534

Feto-maternal haemorrhage associated with genetic amniocentesis: results of a randomized trial

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Summary. Maternal serum alpha-fetoprotein (AFP) levels were determined before and after genetic amniocentesis (n=283) or ultrasound scan (n=268) in a group of women participating in a randomized trial of genetic amniocentesis. Increases in AFP levels were seen significantly more often after amniocentesis than after ultrasound scan (P<0·001) and 48 women in the amniocentesis group had increases in AFP (ΔAFP) that were larger than the maximum ΔAFP (±25 μg/l) seen in the ultrasound group. If a ΔAFP of >25 μg/l represents a feto-maternal haemorrhage (FMH) attributable to amniocentesis, the rate of amniocentesis-induced FMH was 17%. Such FMH was seen significantly more often after transplacental amniocentesis or after amniocentesis performed by less experienced operators. No association was detected between birthweight and FMH attributable to amniocentesis.

Feto-maternal haemorrhage (FMH) has been shown to occur 'spontaneously' throughout pregnancy with a prevalence that increases with gestational age (Freese & Titel 1963; Schröder 1975). The most sensitive method to diagnose FMH in the second trimester is the demonstration of changes in the level of maternal serum α-fetoprotein (AFP) (Lachman *et al.* 1977; Lele *et al.* 1982).

It seems probable, that genetic amniocentesis may cause a FMH. The proportion of women with altered serum AFP levels in association with genetic amniocentesis has been reported to be between 4·9% (Mennuti *et al.* 1983) and 21% (Thomsen *et al.* 1983).

The present study is the first randomized study to assess the frequency of FMH attributable to amniocentesis. Women in the control group had maternal serum AFP determinations done before and after ultrasonography. Another purpose of the study was to test the hypothesis (Thomsen *et al.* 1983) that a FMH during amniocentesis is associated with a reduction in fetal birthweight.

Subjects and methods

Sample size

The size of the study was determined as approximately 600 women, in order to test whether a FMH during amniocentesis was followed by a reduced fetal birthweight (Thomsen *et al.* 1983). It was hypothesized that 20% of the women having amniocentesis would have a FMH. We tested for a minimum difference in birthweight of 200 g, using the 700 g variance on the birthweights found in the first 2000 women partici

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Table 1. Clinical data for the study group, who had an amniocentesis, and the control group, who had an ultrasound scan

	Study group (amniocentesis) (*n*=283)		Control group* (ultrasound) (*n*=268)	
	n	%	*n*	%
Higher social classes	129	45·6	125	46·6
Smokers	120	42·4	117	43·7
Threatened abortion in the present pregnancy	16	5·6	13	4·8
Placental location				
anterior	133	47·0	133	49·6
posterior	138	48·8	113	42·2
other	12	4·2	22	8·2
Placenta perforated	58	20·5		—
Miscoloured amniotic fluid	7	2·5		—
Maternal serum AFP level before procedure (MoM)				
25th centile	0·78		0·79	
median	1·00		1·05	
75th centile	1·33		1·43	
Maternal age (years)				
mean (SD)	28·6	(2·7)	28·3	(2·5)
Parity				
median (range)	1	(0–4)	1	(0–5)

* Data on amniocentesis for seven control patients are not included.

MoM, Multiples of the median for the appropriate gestational week.

pating in our randomized study of genetic amniocentesis (power 80%, level of significance 5%) (Tabor *et al.* 1986).

Subjects

The women in the present study were recruited from a population of 4606 women, aged 25–34 years, without any known increased risk of having a child with a chromosome abnormality or neural tube defect, who participated in a randomized trial of genetic amniocentesis between 1980 and 1984 (Tabor *et al.* 1986). From 1st September 1983, until 31st May, 1984, 600 consecutive women with singleton pregnancies were asked to give a blood sample before and after amniocentesis (*n*=303, study group) or before and after an ultrasound scan (*n*=297, control group. Fifteen women (three in the study group and 12 in the control group) did not wish to participate in the study. Eight women (four in each group) changed their mind after randomization and did not come for the planned examination. Because of organizational mistakes, eight women (four in each group) only gave a blood sample after amniocentesis/ultrasound scan, while 18 (nine in each group) had no blood samples taken at all. The number of women participating in the present study was thus reduced to 283 in the study group having amniocentesis and 268 in the control group having an ultrasound scan. There was no difference between the two groups regarding maternal age, parity, social group, smoking habits or incidence of threatening abortion in the present pregnancy (Table 1).

Amniocentesis. This was performed under real-time ultrasound guidance, using the 'full bladder technique', without anaesthesia and under sterile conditions. Transplacental puncture was avoided, if possible. The mean gestational age at the time of amniocentesis was 16·1 weeks (range 14–19), based on gestational length since the last menstrual period combined with estimation of biparietal diameter. Amniocentesis was performed by one very experienced and three less experienced doctors. Amniotic fluid examination included AFP determination and fetal karyotyping.

Ultrasound scan. A dynamic grey-scale sector scanner was used to assess biparietal diameter, placental location and fetal malformations. The scans were performed by two highly trained nurses. The mean gestational age at the time of ultrasound scan was 18·1 weeks (range 14–23). This gestational age was chosen in order to optimize the detection of fetal defects (J. Bang, personal observation).

Blood samples for maternal serum AFP determination. These were obtained immediately before and 15–45 min after amniocentesis or ultrasound scan from alternate arms. Complete mixing in the maternal circulation has been shown to occur in the first 5–15 min (Horacek *et al.* 1976; Lachman *et al.* 1977). The samples were marked before and after, and analysed 'blind' in the laboratory. Serum AFP was determined using polyethylene glycol radioimmunoassay kits from Amersham (Kjærsgaard & Nørgaard-Pedersen 1979). The two samples from each patient were analysed in the same assay run. The within-assay coefficient of variation was 4% over the range 30–150 µg/l, but higher for values outside this interval. A FMH was estimated to have

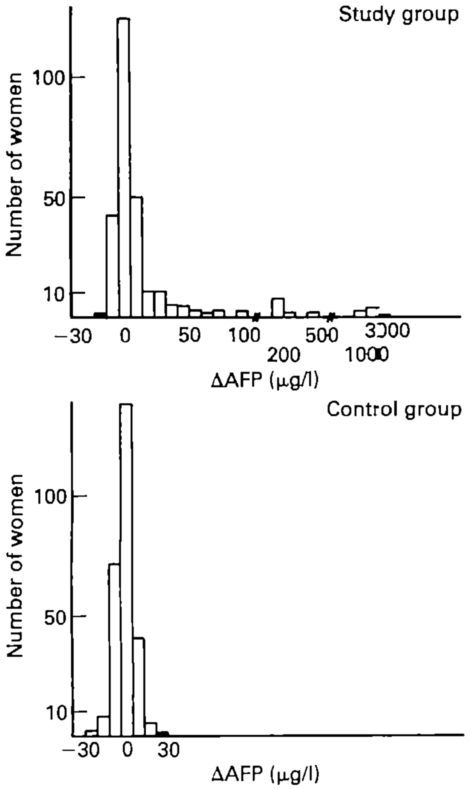

Fig. 1. Difference between serum AFP levels before and after amniocentesis (study group) or ultrasound scan (control group)

occurred on the basis of absolute increases in maternal serum AFP, as this more closely reflects the FMH than percentage increases above the level of maternal serum AFP before amniocentesis/ultrasound scan.

As mentioned above, the maternal serum AFP samples were taken at different mean gestational ages in the study group (16·1 weeks) and in the control group (18·1 weeks). The fetal:maternal serum AFP concentration gradient decreases during the second trimester of pregnancy, as the AFP concentration decreases in fetal serum and increases slightly in maternal serum (Ruoslahti & Hirai 1978). However, the AFP concentration is very much greater in fetal serum (approximately 55 000 times greater in the 16th week and approximately 40 000 times greater in the 18th week) than in maternal serum at the stage of pregnancy involved.

Outcome of pregnancy was recorded from the woman's and infant's charts after delivery or abortion. No woman was lost to follow-up.

Statistics

To compare serum AFP levels in the study with those in the control group, the maternal serum AFP values were expressed as multiples of the median (MoM) for the appropriate gestational week. The Wilcoxon rank sum test was used to compare the distribution of changes in maternal serum AFP in the study group and in the control group. The mean birthweights of the newborn infants were compared using the *t*-test. Otherwise the results were analysed using the χ^2-test.

Ethics

The study was accepted by the ethics committee of the city of Copenhagen.

Results

Maternal serum AFP before amniocentesis/ ultrasound scan

There was no difference between the study and control groups regarding the distribution of maternal serum AFP levels before amniocentesis/ultrasound scan (Table 1) Eleven women (3·9%) in the study group and 11 women (4·1%) in the control group had serum AFP levels above 2 MoM. In the control group, seven women (2·6%) were referred to amniocentesis because of elevated (>2 MoM) maternal serum AFP levels on two occasions. Amniotic fluid AFP was normal in these seven women, as well as in all the women in the study group. No fetuses or infants with neural tube defects were found in this study.

Changes in maternal serum AFP (ΔAFP)

There was a significant difference in the distribution of changes in maternal serum AFP (ΔAFP) between the study and the control groups ($P<0{\cdot}001$) (Fig. 1). The distribution of percentage change in serum AFP was also significantly different ($P<0{\cdot}001$); increases between 20 and 40% were seen in 30 women in the study group and in six in the control group, increases between 40 and 50% were seen in four and three women, respectively. Increases of >50% were seen in 44 women in the study group, but in none of the control group.

Regarding the amniocentesis procedure in the study group, there was a trend towards an association between perforation of the placenta and

Table 2. Outcome of pregnancy

	Study group (n=283)		Control group (n=268)	
	n	%	*n*	%
Spontaneous abortion	4	1·4	2	0·7
Induced abortion	2	0·7	0	
Stillbirth	3	1·1	1	0·4
Livebirth				
Term	263	92·9	254	94·8
Preterm	11	3·9	11	4·1
Low birthweight (≤2500 g)	16	5·8	12	4·5
Small-for-gestation	27	9·8	15	5·7
Gestational age (weeks)				
mean (SD)	38·8	(1·9)	38·8	(1·7)
Birthweight (g)				
mean (SEM)	3382·8	(35·6)	3442·1	(32·9)

the ΔAFP ($0{\cdot}10<P<0{\cdot}20$), but no association between location of the placenta and the ΔAFP. The most experienced doctor caused a ΔAFP significantly less often ($P<0{\cdot}05$). Gestational age at the time of amniocentesis was not correlated with the ΔAFP.

Considering the tail of women in the study group with a larger ΔAFP than the maximum ΔAFP observed in the control group (±25 μg/l; Fig. 1): 48 women (17%, 95% confidence limits 12·6–21·4) in the study group had a ΔAFP>25 μg/l, which was the greatest negative as well as positive ΔAFP found in the control group. In these 48 women, amniocentesis had been done significantly more often transplacentally ($P<0{\cdot}05$) and by less experienced doctors ($P<0{\cdot}05$) than in the 235 women with a smaller ΔAFP.

Outcome of pregnancy

Table 2 shows the outcome of pregnancy in the two randomized groups. The total rate of fetal loss was 2·5% in the study group and 1·1% in the control group ($0{\cdot}20<P<0{\cdot}30$). The outcome of pregnancy in relation to the ΔAFP is shown in Table 3; data for the 48 women in the study group with a ΔAFP>25 μg/l are shown separately. There were no statistically significant differences in the outcomes of pregnancy between the three groups.

All rhesus-negative women had a negative antibody test before amniocentesis or ultrasound scan. Two women developed rhesus-antibodies after amniocentesis: One of them had shown a large increase in maternal serum AFP, the other none. No woman in the control group was isoimmunized.

Of the eight women with a very large ΔAFP (Fig. 1), one had a missed abortion in the 19th week (20 days after amniocentesis), the other seven had live term deliveries. Two infants were small-for-gestation, and another infant was treated for mild haemolytic disease of the new-

Table 3. Outcome of pregnancy in relation to increase in maternal serum AFP

	Study group (amniocentesis)				Control group (ultrasound scan)	
	ΔAFP>25 μg/l (n=48)		ΔAFP≤25 μg/l (n=235)		ΔAFP≤25 μg/l (n=268)	
	n	%	*n*	%	*n*	%
Spontaneous abortion	1	2	3	1·3	2*	0·7
Induced abortion	0		2	0·8	0	
Stillbirth	1	2	2	0·8	1	0·4
Livebirth						
Term	45	94	218	92·8	254	94·8
Preterm	1	2	10	4·3	11	4·1
Small-for-gestation	5	10	22	9·4	15	5·7
Gestational age (weeks)						
mean (SD)	38·8	(1·5)	38·8	(2·0)	38·8	(1·7)
Birthweight (g)						
mean (SEM)	3493·3	(98·9)	3360·3	(37·8)	3442·1	(32·9)

* One woman had an amniocentesis because of elevated maternal serum AFP levels on two occasions.

Table 4. The frequency of feto-maternal haemorrhage (FMH) during amniocentesis, as measured by changes in maternal serum AFP (Δ AFP)

		Women with FMH			
Study	*n*	*n*	(%)	ΔAFP	Ultrasonography
Lachman *et al.* (1977)	58	12	(20·7)	40%	None
Nitowsky *et al* (1978)	71	11	(15·5)	20%	B-scan
Hay *et al.* (1979)	137	14	(10·2)	40%	B-scan
Lele *et al* (1982)	86	6	(7·0)	40%	Real-time
Mennuti *et al.* (1983)	429	21	(4·9)	40%	Real-time
	344	31	(9·0)		B-scan
Thomsen *et al* (1983)	229	48	(21·0)	20%	Ultrasound guidance

born (rhesus antibodies had first been detected in the 29th week of pregnancy).

Of the seven women in the control group who had an amniocentesis because of elevated serum AFP on two occasions, one had a spontaneous abortion and the other six had normal term deliveries.

The gestational age and birthweight of the infants, the number of low birthweight infants (≤2500 g) and the number of small-for-gestation infants were not correlated with an increase in maternal serum AFP. The status of the infants at birth and the number of infants who had neonatal complications were not related to the size of ΔAFP. No needle marks or other injuries, which might be attributed to the amniocentesis, were found in the infants in the study group.

Discussion

The aim of the present randomized study was to determine the rate of FMH caused by genetic amniocentesis. The difference between the study and control groups was that women in the study group had an ultrasound-guided amniocentesis, while women in the control group had a plain ultrasound scan. The women in the two groups were subjected to the same postural changes. In the control group, the ΔAFP may be caused by intra-assay variations, a 'spontaneous' FMH or a FMH related to the ultrasound scan. As the ΔAFP in the control group were small and evenly distributed around 0, they can probably be ascribed to intra-assay variations. We have therefore attributed those ΔAFP values in the study group, that were greater than the largest observed ΔAFP in the control group (±25 μg/l), to an amniocentesis-related FMH. The small difference between the mean gestational age at the time of ultrasound scan in the control group (18·1 weeks) and the mean gestational age at the time of amniocentesis in the study group (16·1 weeks) should not bias our results, since the AFP concentration gradient from fetal serum through amniotic fluid to maternal serum remains very steep up to the 24th week (Ruoslahti & Hirai 1978). As the non-amniocentesis related ΔAFP was determined in the 18th week, where the median serum AFP concentration (62 μg/l) is slightly higher than in the 16th week (50 μg/l), we may have made a very slight underestimation of the amniocentesis-related ΔAFP in the 16th week.

Using our criterion for determining the rate of FMH, we find that this occurred in 48 women (17·0%, 95% confidence limits 12·6–21·4) in the study group. This rate of amniocentesis-induced FMH is in the upper range of those reported in other studies, which estimated the rate of FMH by comparing maternal serum AFP values before and after amniocentesis (Table 4). As these studies were uncontrolled, the rate of FMH was estimated on the basis of percentage increases in ΔAFP. As can be seen from Table 4, the definition used to determine whether a FMH had occurred was not the same in all these studies. Although the different limits may in part reflect the different assay variations of AFP determination, the highest rates of FMH were generally found in those studies using the smallest, i.e. a 20%, increase as criterion for a significant FMH. If we had used this limit, 3.4% of the control group and 27·6% of the study group would have had a FMH, whereas the rate of FMH would have been 17·0% in the study group and 1·1% in the control group using an increase of 40% as limit for a significant FMH.

FMH in connection with amniocentesis has been shown to occur more often with anterior placenta (Bartsch *et al.* 1984; Nitowsky *et al.*

1978; Thomsen *et al.* 1983). This association was not confirmed in the present study, but we found an association between transplacental taps and FMH. This apparent discrepancy reflects the more precise information obtainable when the amniocentesis is done under ultrasound guidance, as was the case in our study.

Mennuti *et al.* (1983) found a significant increase in the risk of abortion from 1·5% among 692 women without FMH to 12.8% in 47 women with FMH. Although our total rate of fetal loss may show a similar trend, the number of spontaneous abortions and stillbirths in the present series is too small to draw any conclusions about a causal relationship between a FMH during amniocentesis and an increased rate of fetal loss. In our total randomized study, comprising 4606 women (Tabor *et al.* 1986), the abortion rate was significantly higher in the study group (1·7%) than in the control group (0·7%). However, it is not known whether this increased abortion rate after amniocentesis correlates with a FMH during amniocentesis.

Regarding the outcome of pregnancy, Thomsen *et al.* (1983) showed that an increase in maternal serum AFP after amniocentesis was associated with a significantly lower mean infant birthweight. We could not confirm this finding, nor that FMH may be associated with a trend towards an increased rate of small-for-gestation infants (Thomsen *et al.* 1983). However, the number of small-for-gestation infants in the whole study group was significantly larger than in the control group. This suggests a causal association with the amniocentesis, but may also be a chance finding.

The possible causal relationship between a FMH during amniocentesis and development of rhesus-immunization was not supported by the present study: of the two women, who developed anti-D after amniocentesis, only one had a FMH during amniocentesis.

Thus, although a FMH occurred in approximately one in every six women having amniocentesis, this did not seem to adversely affect the pregnancy. Possibly, this is because FMH is a rather common event in pregnancy, occurring spontaneously in 10% (Clayton *et al.* 1964) to 20% (Freese & Titel 1963) of all women in the second trimester, as estimated by the admixture of fetal cells to maternal blood. The origin of what we have so far called FMH is still unknown, but may be either transfusion of fetal blood or of amniotic fluid. Therefore, some of the smaller ΔAFP may have been caused by leakage of amniotic fluid through the 'pores' in the amnion (Haddow *et al.* 1979), while the very large ΔAFP may have been caused by a true feto-maternal transfusion (Dallaire *et al.* 1980). Interestingly, among the 48 women in the study group with a ΔAFP larger than the maximum ΔAFP in the control group, as many as four of the eight pregnancies with ΔAFP>500 µg/l were somehow adversely affected, compared with only five of the other 40 pregnancies.

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Received 24 April 1986
Accepted 2 September 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 535–538

Prolactin measurement in the investigation of infertility in women with a normal menstrual cycle

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Summary. Basal serum prolactin concentrations were compared with mid-luteal serum progesterone concentrations and prospectively studied conception rates up to 12 months in women with otherwise unexplained infertility including a normal menstrual cycle. There were altogether 188 women with mean prolactin levels up to 3075 mU/l: 47 with prolactin up to 200 mU/l, 100 with prolactin 201–400 mU/l, 18 up to 600 mU/l, 16 up to 800 mU/l, and 7 greater than 800 mU/l. There were no significant differences in the mean progesterone values or chance of conception between any of the groups. The findings indicate that prolactin measurement is generally of no value in normally menstruating women, except possibly in the unusual event of evidence of persistent distinct luteal deficiency (not found in the present study).

The diagnosis of hyperprolactinaemic amenorrhoea and treatment to induce ovulation are completely reliable. By contrast, in infertile women with a normal menstrual cycle the significance of hyperprolactinaemia, which is usually mild in such cases, is unclear. However, prolactin levels have been shown to be significantly lower in conception than in non-conception cycles in such women (Lenton *et al.* 1979; Glazener 1984), giving rise to the possibility of relative hyperprolactinaemia occurring within the normal range, reducing but not abolishing fertility. Bromocriptine has therefore been used to treat women with unexplained infertility (Lenton *et al.* 1977) but controlled study has demonstrated no benefit from it (Wright *et al.* 1979).

The aim of the present study was to determine the predictive value of prolactin measurement for future fertility by prospective study of the related conception rates without treatment In addition, because infertility in normally menstruating women associated with hyperprolactinaemia has been attributed to luteal deficiency (reflecting follicular disorder) (Bahamondes *et al.* 1979; del Pozo *et al.* 1979) prolactin was studied in relation to luteal progesterone levels.

Patients and methods

The study included a consecutive series of patients with at least 1 year's infertility who were attending the Bristol fertility clinic, with the following provisions. All the women had a normal menstrual cycle (21–35 days) with normal basal serum thyroid hormone and follicle stimulating hormone (FSH) levels. Other fertility factors were normal as judged by laparoscopy (performed only if conception still failed after 6–12 months), semen analysis, postcoital sperm-mucus penetration and coital frequency. None of the women was receiving any drugs to stimulate ovulation, nor any dopamine agonist or antagonist. The serum progesterone concentration was measured in the mid-luteal phase, checked retrospectively as 5–10 days before the following menstrual period in three

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cycles or only two if both samples were similar in value.

Blood samples were obtained by routine venepuncture method with disposable No. 1 gauge needles at first attendance at the clinic, after physical examination, although no attempt was made to express secretion from the breasts. Serum was stored at 4°C for no more than a few days before assay, which was done as routine. If the prolactin concentration was >400 mU/l measurement was repeated in another one or two samples. If then the level was found to be >400 mU/l in only the first sample it was ignored, otherwise the mean from all samples was taken as the value in the study.

Prolactin was measured by radioimmunoassay in duplicate samples, run concurrently with an MRC standard (International Reference Preparation 75/504). Iodinated prolactin and rabbit antibody were used, with donkey anti-rabbit-antibody for separation. Samples were assayed in different batches as routine, the mean inter-assay coefficient of variation being 10·8%. Progesterone was measured by specific radioimmunoassay as described elsewhere (Hull *et al.* 1982) also as routine, the inter-assay coefficient of variation being 12·5%.

Cumulative conception rates were calculated as for life-table analysis, which allows for some patients who continued longer than others in the study. The time of observation was taken from first attendance at the clinic and continued up to 12 months. Conception rates were compared between groups divided into bands of prolactin values throughout the range by the z-test for proportions. Mid-luteal progesterone values were compared with the prolactin values (after log-transformation of the latter) by linear regression analysis, and mean progesterone values were calculated in the banded prolactin groups (to take particular account of the extreme groups) and compared using Student's t-test.

Results

The study included 188 patients with a median age of 28 years (range 18–41) and median duration of infertility of 18 months (12–144), of whom 41% were parous. After grouping the patients by their prolactin values there were no significant differences in age of duration of infertility between them. Table 1 shows that there were no significant differences between any of the groups in either their mid-luteal progesterone levels or conception rates. Linear regression analysis also revealed no significant relation of progesterone to prolactin levels. The conception rates appeared to be considerably lower in the patients with prolactin levels in the range 601–800 mU/l than in the other groups with lower or higher prolactin levels, but the differences were not significant, even after combining the results in all groups with lower prolactin levels. In the latter groups combined (prolactin up to 600 mU/l) the conception rate was 38·0% (SE 4·3) at 6 months and 47·7% (SE 5·1) at 12 months.

In the group of patients with prolactin levels >800 mU/l, four had a (mean) prolactin value >1000 mU/l (1033, 1533, 1660, 3075 mU/l) and of those, two conceived during the study without treatment (the first and fourth respectively). In the fourth patient, who conceived, the individ-

Table 1. Mean mid-luteal serum progesterone concentrations and cumulative conception rates in normally menstruating infertile women related to their serum prolactin concentrations

Prolactin (mU/l)	No of patients	Progesterone* (nmol/l), mean (SD)	Cumulative conception rates (%) mean (SE) 6 months	12 months
<200	47	39·7 (11·7)	29·0 (8·0) (n† = 32)	41·0 (10·0) (n† = 24)
201–400	100	41·6 (13·1)	42·0 (5·4) (n = 84)	49·2 (6·2) (n = 64)
401–600	18	44·2 (6·8)	36·3 (12·8) (n = 14)	57·5 (16·5) (n = 9)
601–800	16	36·0 (8·2)	25·5 (11·3) (n = 15)	25·5 (17·8) (n = 6)
>800	7	42·0 (27·8)	42·9 (20·2) (n = 6)	61·9 (21·7) (n = 5)

* The representative progesterone concentration for each patient was calculated as the mean of all mid-luteal measurements available per patient.

† n = the number of patients who actually continued to the relevant end-point (6 or 12 months) including those who conceived earlier.

ual prolactin measurements were 2676 and 3474 mU/l (mean 3075 mU/l).

Discussion

This study demonstrates lack of correlation between prolactin levels and luteal function as assessed by luteal progesterone production, and between prolactin and the chance of conception, in infertile women with a normal menstrual cycle. In another study we also found lack of correlation between the prolactin response to intravenous thyrotrophin releasing hormone and the chance of conception in otherwise normal women with borderline hyperprolactinaemia (Glazener 1984).

Although the observed conception rates were higher in women with prolactin levels <600 mU/l than above this level, the rates were again higher in women with prolactin levels >800 mU/l and even >1000 mU/l. One patient with prolactin levels about 3000 mU/l also conceived without treatment. We therefore conclude that the observed (but statistically insignificant) reduction in conception rates in the women with prolactin levels in the range 601–800 mU/l was due to chance.

Our findings show that the normal range of prolactin has a skewed distribution with a long upper tail that overlaps to a considerable extent with the abnormal range found in women with amenorrhoea. In a related study of untreated patients with normal menstrual cycles we have found, using log-transformation of the data, that the mean and 95% population limits of prolactin in non-conception cycles were 290 mU/l and 90–940 mU/l respectively, and the findings were similar in conception cycles, being 237 mU/l and 47–1200 mU/l (Glazener 1984). The need to appreciate the skewed distribution has been emphasized by Jeffcoate (1978) and Lenton *et al.* (1979), who concluded that the normal upper limit is at least 800–1000 mU/l.

Possible explanations for high levels of prolactin found in normal fertile women include spurious elevation due to natural fluctuation in levels, response to stress, or breast examination or irrelevant isomers of prolactin. The effects of normal episodic secretion, stress and examination should not, however, be clinically misleading according to studies, respectively, by Daggett & Nabarro (1979), Whittaker *et al.* (1982), and Jarrell *et al.* (1980). In the present study, all patients with prolactin levels >400 mU/l had repeated measurements to minimize the likelihood of misleading high levels. The value of blood sampling from an indwelling cannula in resting patients to achieve truly 'basal' values has not been shown to improve on merely repeating the sample. Very high levels in normal women are more likely to be due to the presence of immunoreactive molecular forms (notably 'big, big prolactin') that are biologically inactive *in vivo* (Andersen *et al.* 1982).

Although the normal and abnormal ranges of prolactin overlap, for various reasons, the essential practical conclusion is that the menstrual state provides the most reliable index of true hyperprolactinaemia. This is further supported by the clinical response to bromocriptine therapy, which is highly effective in amenorrhoeic women but which we have found to be ineffective in menstruating women (Glazener 1984).

On the other hand, it seems clear that hyperprolactinaemia can cause luteal deficiency and infertility in women with normal menstrual cycles, although infrequently and with only borderline elevation in prolactin making the diagnosis practically almost impossible in individuals. That it can occur is confirmed by presentation as an early phase in the natural evolution of hyperprolactinaemic amenorrhoea (Bahamondes *et al.* 1979), and in some women following incomplete surgical removal of a pituitary prolactinoma resulting in return of menstruation but with luteal deficiency that responds reliably to bromocriptine therapy (Hull, 1983).

The only other convincing evidence for hyperprolactinaemia causing persistent luteal deficiency and associated infertility, backed up by responsiveness to bromocriptine, was in a small uncontrolled study reported by del Pozo *et al* (1979). Other reports of infertility attributed to nocturnal hyperprolactinaemia (Board *et al.* 1981), intermittent borderline hyperprolactinaemia (Coutts *et al.* 1979), and midcycle hyperprolactinaemia (Ben-David & Schenker 1983) remain unproven and unconvincing. Properly controlled therapeutic trials with bromocriptine in normally menstruating women with apparent hyperprolactinaemia are still required.

In summary, our results in normally menstruating women suggest no evidence of reduction in fertility caused by relative hyperprolactinaemia within the normal range of prolactin or even when marginally elevated (800–1000 mU/l). The results were similar with grossly raised prolactin levels, although a larger number of women is needed for study to be fully confident of that group. We conclude that true hyperprolactinaemia almost invariably disturbs the menstrual cycle, and in women with a normal cycle the finding of normal luteal progesterone levels probably excludes any significant interference with fertility by apparent hyperprolactinaemia.

Acknowledgments

We are grateful to the South Western Regional Health Authority Medical Research Committee and Sandoz Products Ltd for financial support for Dr Glazener, to the Departments of Clinical Chemistry at the Bristol Royal Infirmary and Southmead Hospital for prolactin and progesterone measurements and to Dr A. O. Hughes, University of Bristol Department of Epidemiology and Community Medicine for statistical advice. The information contained in this paper is from an MD Thesis by Dr Glazener in the University of Bristol.

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Received 20 May 1986
Accepted 28 February 1987

British Journal of Obstetrics and Gynaecology
June 1987, Vol 94, pp 539–542

'Unexplained infertility' results of secondary investigations in 95 couples

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Summary. Abnormalities of in-vitro sperm-mucus penetration, ovarian hormone deficiency, specifically poor progesterone surge, and luteal cyst formation were assessed prospectively in 95 couples with fully investigated primary infertility of ≥3 years duration. Abnormal sperm-mucus penetration was found in 22, half of whom could have been identified on semen assessment alone. Ten other males had recurrent oligospermia but with normal motility and mucus penetration. Twenty-one patients had a poor progesterone surge and seven of them demonstrated retained luteal phase cysts. Endocrine and mucus penetration abnormalities did not coincide, demonstrating that they are distinct and unrelated phenomena. A significant number of couples were found for whom the term 'unexplained infertility' was no longer applicable and appropriate management could be considered.

When infertile couples are fully assessed by current routine investigations, no aetiological factor can be found for 24–28% of them (Templeton & Penney 1982; Hull *et al.* 1985).

Other factors in 'unexplained' infertility may include regular but abnormal ovulation and abnormal sperm-mucus interactions, luteal phase deficiency (Jones 1949; Jones *et al.* 1974; Soules *et al.* 1977) and abnormal luteal phase hormone profiles. Following the luteinizing hormone (LH) surge, a poor progesterone surge was found in 38% of cycles studied in patients with unexplained infertility of more than 3 years duration (Coutts *et al.* 1978). Abnormal sperm-mucus penetration has been identified in a small number of such couples (Matthews *et al.* 1980; Zegers *et al.* 1981; Templeton *et al.* 1982) and has been suggested to coexist with abnormal hormone profiles (Roumen *et al.* 1982)

In this unit, after initial investigations, 30% of 822 couples with primary infertility showed no abnormality and a prospective study was undertaken to determine the incidence and coincidence of abnormal hormone profiles and abnormalities of in-vitro sperm-mucus penetration in an homogenous group of couples with long-standing infertility, fully assessed according to a fixed protocol.

Patients and methods

Ninety-five couples with primary infertility of average duration 6·5 years (range 3–14) were included in the study. The average age of the women was 31 years (range 25–42) and that of the men 33 years (range 26–52). Fifty-one couples (53·7%) were initially investigated in

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other gynaecological units. All the couples met the following criteria: (i) normal menstrual rhythm; (ii) normal pelvic organs and tubal patency assessed by laparoscopy; (iii) ovulation determined by mid-luteal serum progesterone level >30 nmol/l; (iv) previous reported semen analysis (count $>2 \times 10^7$/ml and motility >40%); (v) an interval of at least 12 months between laparoscopy and the start of investigations.

All the women had blood taken daily during a complete menstrual cycle. Each blood sample was subsequently assayed for LH, follicle stimulating hormone (FSH), progesterone and 17β-oestradiol (E_2) by specific radioimmunoassays. All individual patient samples were analysed within single assays (Acar *et al.* 1980). When progesterone concentrations fell below the laboratory normal range on at least three occasions between days +1 and +6 (the day of the LH surge being day 0), a poor progesterone surge (PPS) was diagnosed (Coutts *et al.* 1978).

A quantitative assessment of the early luteal phase progesterone profile was calculated for each cycle using a progesterone index (PI) derived from a comparison with our normal laboratory data over days +2 to +6. Values below 70 indicated subnormal early luteal phase progesterone concentrations, based upon normal ranges established in 12 volunteers (Coutts 1985).

Ovarian ultrasonography was performed using the full bladder technique (Adam 1981). Follicular diameter estimation was regularly undertaken during the periovulatory phase to assess follicular growth and in the luteal phase to study the occurrence of retained luteal phase cysts (Coutts *et al* 1982).

Endocervical mucus was extracted and investigated when the leading follicle was between 18 and 21 mm in diameter. The cervix was cleaned and swabbed with sterile water as appropriate. Mucus quality and quantity were assessed using a simple scoring system (Insler *et al.* 1972). Mucus was drawn into a tuberculin syringe and transferred directly to a 75 mm capillary tube (volume 60 µl). Further tubes were prepared for retesting and cross-testing as necessary. The capillary tube was inserted into a small reservoir of test semen and incubated at 37°C for 30 min in a humid environment.

Sperm penetration tests were assessed using a microscope × 10 magnification and penetration of >2 cm was accepted as normal. Full seminal analysis was undertaken concurrently.

Abnormal sperm penetration tests were repeated at the appropriate time in subsequent cycles and crossover tests, using normal donor mucus and fresh or frozen donor semen, were performed when tests were repeatedly abnormal In such cases seminal plasma and serum from both partners were assessed for circulating agglutinating antisperm antibodies using the microtray agglutinating test described by Friberg (1977) and cytotoxic antibodies using a microimmobilization method (Isojima *et al.* 1968).

Results

Table 1 shows the frequency and distribution of abnormal ovarian hormone profiles, luteal cysts and sperm penetration abnormalities in the 95 infertile couples. One third of the abnormal luteal phase progesterone profiles were associated with retained luteal phase cysts (Coutts *et al.* 1982).

Abnormalities of sperm penetration were found in 22 cases and subnormal luteal progesterone profiles (PI <70) were seen in 21.

Table 1. Abnormal hormone profiles, luteal cysts and abnormal sperm-mucus penetration in 95 couples with unexplained infertility

Hormonal profile	No. of couples *n* (%)	PI		No with abnormal sperm-mucus penetration
		Mean (SD)	Range	
Normal	73 (76·8)			22
Normal and luteal cyst	1 (1·0)			—
PPS	14 (14·7)	53 (19)	32–69	—
PPS and luteal cyst	7 (7·4)	45 (10)	32–64	—
Total	95 (100)			

PPS, Poor progesterone surge; PI, progesterone index (Coutts 1985)

Table 2. Factors associated with abnormal sperm-mucus penetration in 22 couples.

Factor	No.	(%)
Azoospermia	1	(4·5)
Asthenospermia	5	(22·7)
Male antibodies	5	(22·7)
Mucus hostility	7	(31·8)
No mucus	4	(18·2)

There was no case of coincidence of the two observations. Two patients with PPS had partners with recurrent oligospermia (range 13–18 million/ml) but with normal motility and mucus penetration.

Sperm-mucus interactions

Thirty-four (35·7%) of the couples assessed showed abnormalities of sperm-mucus penetration at the first test and 22 (23·1%) had abnormal repeat tests (Table 2). The patients with asthenospermia had recurrent low motility (<10%) on fresh (<2 h) abstinence specimens of semen. In the cases where male antibodies were thought to be significant, the serum and seminal plasma were both positive for agglutinating antibodies (range $^1/_{32}$–$^1/_{2040}$) but negative for immobilizing antibodies. In each case there was gross agglutination on simple analysis and failure of sperm penetration with partner and donor mucus.

Minor degrees of sperm agglutination were present in a few other cases, but sperm mucus penetration was unaffected and none had a significant antisperm antibody titre.

All patients with confirmed mucus hostility had high quality mucus with an Insler score >9 (Insler *et al.* 1972). In all cases there was failure of sperm penetration with both partner and donor semen, and the semen samples showed no antisperm antibodies.

No mucus was obtained from four patients despite attempted mucus extraction on up to six occasions. None had a history of cervical surgery or treatment and periovulatory E_2 levels were normal in each case (laboratory range 600–1200 pmol/l).

In addition, there were eight males with recurrent oligospermia (range 7–18 million/ml) but with normal motility and mucus penetration.

Discussion

This study shows that abnormal sperm-mucus interaction is a significant factor in strictly defined 'unexplained' infertility. The aetiology was unclear in some cases but abnormal ovarian function was not contributory. Abnormal ovarian function, as shown by PPS, was also an important factor in 21 (23%), and a third of them showed associated abnormal patterns of follicular growth and corpus luteum formation discernible by ultrasonography.

This proportion of hormonally abnormal cycles was slightly less than that reported for a similar group of patients (Coutts 1985) in which the mean duration of infertility was greater. The coincidence of ultrasound abnormalities was also reduced. In contrast to Roumen *et al.* (1982) our findings showed no coincidence of deficient sperm-mucus interaction with hormone profile abnormalities. Patients with PPS showed normal periovulatory E_2 levels, and normal mucus quantity and quality. Mucus hostility is more likely to have a local immunological basis than abnormal hormone stimulation.

The results of the semen assessment, with approximately 12% of those referred showing abnormalities, confirmed that repeat semen examination should be undertaken (Zegers *et al* 1981), because of the possibility of recently acquired abnormalities.

The men who demonstrated azoospermia, recurrent asthenospermia or agglutination with significant antisperm antibody titres gave no history of trauma or recent illness.

Oligospermia occurred in 10%. All the men had a motile normal sperm density within an accepted normal range described by Hull & Glazener (1984), although it is difficult to avoid the conclusion that the long-standing infertility was caused by this problem.

The patients with no mucus production showed normal follicular phase E_2 profiles. Two of these patients were treated with daily injections of human menopausal gonadotrophins and mucus production and subsequent sperm-mucus penetration were shown to be normal when periovulatory E_2 levels rose to >3000 pmol/l, indicating a possible resistance at endocervical level which may be overcome by exposure to supranormal oestrogen concentrations. Neither patient, however, became pregnant after six cycles of treatment.

When infertility is unexplained, the chance of pregnancy is associated with the duration of infertility (Hull *et al.* 1985). In-vitro fertilization (IVF) has been shown to be successful in such patients (Mahadevan *et al.* 1983; Hull *et al.* 1984), and indeed has been advocated for up to 25% of couples with unexplained infertility (Hull *et al.* 1985).

We have shown that by studying in depth a group of patients with long-standing infertility, a significant number of couples can be found with definable abnormalities. These include PPS which is amenable to therapy (Fleming *et al* 1982; Coutts 1985) and, by excluding easily determined seminal abnormalities, a further group with more subtle defects in sperm transport and potential fertilizing ability may be found for whom IVF should not be the initial therapy and for whom it may not be appropriate (Hull *et al.* 1984).

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Received 3 June 1986
Accepted 12 September 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 543–547

Systematic semen culture and its influence on IVF management

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Summary. Semen specimens from 519 men were cultured for organisms 2 weeks before oocyte recovery for in-vitro fertilization (IVF). The cultures from 72 men contained more than 5000 bacteria/ml and the IVF attempt was postponed. The IVF outcome was assessed in 382 couples in relation to the semen culture result. The pregnancy rate per cycle was significantly reduced when the semen culture contained organisms compared with axenic semen ($P<0{\cdot}05$). This was independent of the cleavage rate of oocytes and the number of embryos transferred. Although mycoplasma was frequently cultured, chlamydial infection was very rare and no viruses were isolated in this study.

Several studies have demonstrated a higher prevalence of infected semen in a population of infertile men than in a fertile reference population (McGowan *et al.* 1981; Toth & Lessel 1981). Bacterial proliferation can modify the fertilizing capacity of spermatozoa (Brun *et al.* 1977). Mettler *et al.* (1982) reported a correlation between the presence of pathogenic bacteria and the degeneration of hamster eggs fertilized by infected human sperm (Mettler *et al.* 1982). Most protocols for in-vitro fertilization (IVF) programmes require a preliminary bacteriological analysis of semen although there have been no publications which indicate how the results modify management. *In vivo,* the presence of micro-organisms is not synonymous with infection; this diagnosis depends upon the nature and concentration of the organisms isolated (Fari 1983; Fari *et al.* 1977).

In our IVF programme between December 1982 and July 1983, a semen sample was always obtained and cultured for organisms at the time of the preliminary consultation for IVF and any infection that was detected was treated. However, as it was not practicable to obtain a semen culture immediately before the IVF cycle, all men were treated prophylactically with doxycycline (Vibramycin, Pfizer, Orsay France) for the 2 weeks preceding oocyte recovery. Despite this therapy there were 15 failures of fertilization in 237 IVF cycles which were associated with evidence of semen infection. We therefore performed a prospective quantitative study, between September 1983 and July 1984, to assess the significance of bacteriospermy and its influence on the success of IVF.

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Subjects and methods

Semen culture

All the men provided a specimen of semen for culture 2 weeks before the IVF treatment. After micturition, the hands and genital region were carefully cleansed and a split ejaculate of semen was collected into sterile containers. After liquefaction at 37°C a portion of the second fraction was mixed with a drop of cresyl blue and examined by direct microscopy. This allowed the demonstration of polymorphs and trichomonads and enabled the flora to be typed according to the Gram reaction. Specific techniques were adopted for Candida (Sabouraud medium), gonococci [Chocolate agar with the addition of Polyvitex VCN (vancomycin, colistin, nystatin)], *Mycoplasma* (A3 medium) and *Ureaplasma urealyticum* (urea broth and urea agar). Chlamydias were demonstrated by the presence of cytoplasmic inclusions in HELA cell cultures Herpes and cytomegalovirus cell cultures were established using VERO cells to observe the characteristic cytopathic effect.

The presence of *Trichomonas, Candida,* gonococci, *Chlamydia,* herpes or cytomegalovirus was taken to signify specific infection regardless of their concentration. *Mycoplasma hominis* and *Ureaplasma urealyticum* were not considered as commensals of the genital tract but were only regarded as a significant cause of infection above a certain threshold concentration. *Staphylococcus epidermis* (coagulase negative staphylococci) and group D streptococci were considered as urethral commensals whereas Enterobacteriaceae, group B streptococci and *Staphylococcus aureus* were not regarded as part of the indigenous urethral flora.

Semen samples for culture were provided by 519 men. Couples were excluded from IVF treatment in that cycle when the semen culture demonstrated >5000 bacteria/ml, $\geqslant 10^3$ mycoplasma or ureaplasma/ml or any organisms characteristic of a specific infection irrespective of their concentration ($n = 72$). Patients were accepted for IVF if the semen culture contained 3000–5000 bacteria/ml and/or $\leqslant 10^2$ mycoplasma or ureaplasma/ml ($n = 82$). However. these men were treated with the appropriate antibiotic, as determined by sensitivity studies, from the time the results became available until the day of oocyte recovery (range 10–21 days). Patients were accepted without treatment if the semen culture contained <3000 bacteria/ml ($n = 68$) or was free of organisms ($n = 232$). These threshold concentrations for bacterial growth were selected based on the studies of Fari *et al.* (1977) and Brunner *et al.* (1983). In the other 65 couples, the IVF attempt was abandoned either because of inadequate response to follicular stimulation or failure to recover oocytes at follicular aspiration or because of intercurrent illness. The technique of IVF was as described previously (Testart *et al.* 1982). In particular, all sperm specimens used for IVF contained at least 5×10^6 normal motile sperm in the ejaculate. The pregnancies were categorized as follows. A biochemical pregnancy was defined as a human chorionic gonadotrophin (hCG) value of >20 m-i.u./ml on two occasions more than 11 days after oocyte aspiration but never exceeding 1000 m-i.u /ml. In fact at hCG levels of $\geqslant 1000$ m-i.u./ml a gestational sac was always detected by ultrasound and the pregnancy had become clinical. If the pregnancy did not proceed it was defined as a spontaneous abortion.

Results

Semen bacteriology

The semen cultures from 72 men contained >5000 bacteria/ml. The organisms most frequently encountered were *Staphylococcus epidermis,* Enterobacteriaceae and mycoplasmas. All the men were treated and where mycoplasmal infection was detected the partner was treated concurrently Semen culture was repeated after completion of the treatment. In 19 men the infection proved resistant to therapy.

In 382 men the semen culture results fulfilled the criteria for inclusion in the IVF cycles. They were subdivided into three groups according to the concentration of bacteria: 232 semen cultures showed no growth (group 1); 68 showed some growth (group 2, 10–3000 bacteria/ml) and 82 showed medium growth (group 3, 3000–5000 bacteria/ml and/or $\leqslant 10^2$ mycoplasma/ml). Table 1 shows the distribution of organisms found in the medium-growth group. *Staphyloccus epidermis* predominated and mycoplasmas were often cultured in association with other organisms.

Chlamydial infection was detected in only one patient. There were no gonococci isolated and no evidence of herpes or cytomegalovirus infec-

Table 1. Frequency of various micro-organisms isolated from 82 semen samples*

Micro-organism	Positive specimens
Staphylococcus epidermidis	29
Enterobacteria:	13
Escherichia coli	9
Proteus	2
Klebsiella	2
Streptococcus	5
D	4
B	1
Candida	1
Staphylococcus aureus	1
Mycoplasma only	13
Mycoplasma associated with other bacteria	36

* Samples contained between 3000 and 5000 bacteria/ml and/or $\leq 10^2$ mycoplasma/ml.

tions was detected in the 500 semen specimens subjected to virological studies.

IVF results and semen bacteriology

The outcomes in the 382 IVF cycles were analysed in relation to the bacteriological findings in the 382 semen samples cultured 2 weeks before IVF. The cleavage rate of the inseminated oocytes was between 72 and 75% in the three groups, the rate did not vary irrespective of the degree of bacterial contamination. However, the proportion of pregnancies initiated was significantly higher in the group with negative semen culture results (48 pregnancies from 232 cycles; 21%) than in the other two groups with positive semen culture (18 pregnancies from 150 cycles; 12%), (χ^2 $P<0.05$) (Table 2). This difference was not related to the number of embryos replaced as this was similar in all three groups (Table 3) There was no difference in the pregnancy rate between the two groups with positive semen culture results, i.e. those patients with 10–3000 bacteria/ml (group 2, untreated) and those with 3000–5000 bacteria/ml (group 3, antibiotic therapy). The outcome of the pregnancies was not related to the semen culture result (Table 2).

During the 11 months period of the study we have recorded no failure of fertilization associated with infection of the IVF culture medium. In a retrospective control period this occurred on 15 occasions in 237 cycles.

Discussion

In this study of systematic semen analysis in IVF patients only 45% (232 of 519) of semen speci-

Table 2. Outcome of pregnancies initiated after in-vitro fertilization (IVF) in relation to bacteriospermy

		Number of pregnancies initiated and outcome			
Bacteriospermy (bacteria/ml)	Number of IVF cycles	Total *n* (%)	Biochemical *n* (%)	Spontaneous abortion *n* (%)	Continuing *n* (%)
0	232	48 (21)*	3 (1)	9 (4)	36 (15)
10–3000	68	8 (12)	1 (1)	2 (3)	5 (7)
3000–5000	82	10 (12)	2 (2)	1 (1)	7 (8)

*Total no. of pregnancies initiated was significantly higher than in the other two groups combined (χ^2, $P<0{\cdot}05$).

Table 3. Distribution of embryo transfer

Bacteriospermy (bacteria/ml)	*n*	Number of embryo transferred		
		1	2	3
0	159	67 (42%)	54 (34%)	38 (24%)
10–3000	41	19 (46%)	15 (37%)	7 (17%)
3000–5000	47	22 (47%)	14 (30%)	11 (23%)

mens were demonstrated to be totally free of micro-organisms. Careful explanation of perineal hygiene and skin preparation before producing the specimen should minimize contamination arising from the skin or external urethral meatus. Our results agree with previous reports that asymptomatic bacteriospermy is not uncommon (Toth & Lessel 1981).

The varieties of bacteria isolated in this study are similar to those described previously (McGowan *et al.* 1981; Busolo *et al.* 1984; Colpi *et al.* 1982). We were surprised to record only one case of chlamydial infection as this organism is often present in sterile couples (Suominen *et al.* 1983) and has been implicated in IVF failure (Moss 1984). However, it is possible that the toxic activity of seminal plasma on the cell cultures may explain the absence of growth reported in our and other studies (Busolo *et al.* 1984). Mycoplasma, in contrast, was a frequent isolate in our patients. This organism is very prevalent in infertile men and couples (Lewis 1981; Foresta 1983; Upadhyaya 1983). The effect of mycoplasmal infection on IVF has not been studied in man, but in the mouse (Swenson 1982) and in the hamster heterologous ovum penetration test (Busolo & Zanchetta 1985), the oocyte fertilization rate is decreased in the presence of this organism.

It was reassuring that no viruses were cultured in the 500 semen samples. This confirms the report by Mettler *et al.* (1982) that viral infections of sperm can be disregarded in relation to IVF.

Neither the presence nor the quantity of bacteria influenced the oocyte fertilization rate in our study. The only previous work on this subject (Hewitt *et al.* 1985) demonstrated a lower oocyte fertilization rate with semen contaminated with pathogenic organisms than with semen containing only commensals or no micro-organisms. Although bacterial concentrations were not estimated in that study, three species were implicated in IVF failure: *E. coli, Proteus mirabilis* and *Staphylococcus aureus*.

Although multiple factors interrelate in the occurrence of an IVF pregnancy, we obtained better pregnancy rates with axenic semen for IVF. This was independent of the oocyte cleavage rate and of the number of embryos transferred. It is not known how the bacteriospermy influences the development of pregnancy. Hewitt *et al.* (1985) have suggested that the organisms may adversely affect the binding of spermatazoa to the zona pellucida or penetration of the oocyte. It has also been shown (Busolo & Zanchetta, 1985) that *Ureaplasma urealyticum* produces a specific factor which hinders the penetration of zona free hamster oocytes by human sperm. However, our results indicate that the fertilization rate is unaffected but the subsequent development of the zygotes appears to be compromised. This could be due to abnormal fertilization or alternatively the presence of bacteria in the uterus, either sexually transmitted or introduced at the time of embryo transfer, may impair embryonic development.

Lewis (1981) suggested that antibiotic therapy may have an additional appreciable effect on sperm characteristics, particularly on motility, but Makler *et al.* (1981) found no change in the criteria of sperm quality with antibiotic therapy. Although we did not investigate the role of antibiotics as such we found no difference in the success of oocyte fertilization or in the rate of pregnancies between treated and non-treated bacteriospermy (<5000 organisms/ml).

We conclude that routine semen culture is necessary before IVF. The threshold levels we have adopted for exclusion from IVF or inclusion with antibiotic therapy appear insufficient as totally axenic sperm is associated with the most favourable IVF outcome. However, as the oocyte fertilization rate was not affected by the presence of bacteria (<5000/ml) a pre-existing sexually transmitted endometritis cannot be excluded. Further studies are in progress to help resolve this problem. Although culture for mycoplasma is necessary, we think it is no longer necessary to culture for *Chlamydia* or viruses.

Acknowledgments

We would like to express our gratitude to Mme Danielle Journo and Mlle Florence Béquet for their secretarial assistance and Mme Monique Volante and Mlle Armelle Gazangel for technical assistance in the IVF laboratory.

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Received 22 May 1986
Accepted 27 October 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 548–553

Oestradiol-17β and progesterone level changes in peritoneal fluid around the time of ovulation

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Summary. In 15 women, peritoneal fluid was obtained by either culdocentesis ($n = 20$) or laparoscopy ($n = 3$), before ($n = 9$) and after ($n = 14$) ovulation. Ultrasound was used for ovulation detection. Before ovulation the mean oestradiol-17β level in plasma and peritoneal fluid was not essentially different; the mean progesterone level was significantly higher in peritoneal fluid. After ovulation both the mean oestradiol-17β and progesterone levels were significantly higher in peritoneal fluid than in plasma. In peritoneal fluid, there was a wide distribution of individual oestradiol-17β values before and after ovulation; no significant difference existed between the mean pre- and postovulatory oestradiol-17β level. More consistent changes were seen in peritoneal fluid progesterone levels; the mean level was significantly higher after ovulation. In three subjects, a low postovulatory progesterone level in peritoneal fluid was associated with a cystic luteal structure observed by ultrasound, suggesting a reduced leakage of fluid from the ovulation stigma.

There are several studies of changes in steroid hormone levels in peritoneal fluid around the time of ovulation (Maathuis *et al.* 1978, Donnez *et al.* 1982; Zorn *et al* 1982).

Authors differ in their assessment of the value of these changes for the retrospective diagnosis of ovulation or the occurrence of a luteinized unruptured follicle (Koninckx *et al.* 1980, Donnez *et al.* 1983, Dhont *et al.* 1984; Lesorgen *et al* 1984)

A basic deficiency in all these studies is that the criterion of ovulation, if determined at all, was an ovulation stigma seen at laparoscopy, which in itself has been demonstrated to be inaccurate (Portuondo *et al* 1981, Vanrell *et al* 1982). Ultrasound has now been accepted as a reliable method for establishing ovulation (Renaud *et al.* 1980; Queenan *et al* 1980; Wetzels & Hoogland, 1982).

The object of the present study was to provide further information on steroid hormone level changes in peritoneal fluid around the time of ovulation with the use of ultrasound for ovulation detection.

Subjects and methods

A total of 15 women consented to participation in the study. The study itself was approved by the ethics review board. There were eight women with unexplained infertility, four infertile

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women with endometriosis, diagnosed by observing endometrial implants at laparoscopy and classified as mild according to the criteria of Acosta *et al.* (1973), and three women with proven fertility who requested reversal of sterilization. All had regular biphasic menstrual cycles.

Ovulation was detected by daily ultrasound measurements of follicular size. These were started 3–4 days before the expected date of ovulation predicted from basal body temperature with or without ultrasound follicular monitoring in previous cycles.

Ultrasound examinations were made with a Pie-Data 900 real-time sector scanner with a 3·5 MHz transducer; a calibrated sound velocity of 1540 m/s was used.

The follicles were measured in three dimensions with electronic calipers. In the parasagittal plane the largest longitudinal and antero-posterior diameter and in the transversal plane, the largest horizontal diameter was measured. From these three diameters the mean was calculated.

Ovulation was defined as a decrease in mean follicular diameter by at least 5 mm or the complete disappearance of the follicle.

It was planned that each of the 12 infertile patients should provide one pre- and post-ovulatory peritoneal fluid sample, collected in two consecutive cycles by culdocentesis, using the Cupido system (Medical Developments and Technology, The Netherlands) (Wiegerinck 1984) This consists of a needle guidance system which is introduced into the posterior fornix. A vacuum is applied for attachment to the vaginal wall. A needle covered by a teflon catheter is subsequently introduced through the needle-guidance system into the cul-de-sac. Following withdrawal of the needle, peritoneal fluid is collected via the catheter.

The primary object for the pre-ovulatory sampling of peritoneal fluid was to compare the value of the spermatozoa-recovery with the post coital test. The peritoneal fluid sample was obtained as near as possible to the day of ovulation, as estimated from ultrasound measurements of follicular size and from the cervical mucus. After collection of peritoneal fluid, daily ultrasound scans were continued until the occurrence and timing of ovulation was confirmed. The primary object of the postovulatory sampling of peritoneal fluid was to compare the value of steroid hormone measurements in this fluid with ultrasound for the diagnosis of a luteinized unruptured follicle.

For the same purpose, in three women requesting reversal of sterilization, a laparoscopy was planned to follow ovulation. However, ovulation occurred later than predicted and pre-ovulatory fluid was collected. All three patients consented to culdocentesis for peritoneal fluid collection after ovulation.

All postovulatory peritoneal fluid samples were collected within 24 h after ovulation was detected by daily ultrasound scans. A final ultrasound scan was performed immediately before the puncture procedure in order to estimate the amount of free fluid in the cul-de-sac.

Plasma was obtained at the time of every peritoneal fluid collection All peritoneal fluid and plasma samples were centrifuged for 10 min at 2500 r/min and the supernatant fluid was then frozen within 30 min after collection To avoid the possibility of extensive contamination of the peritoneal fluid with blood only those peritoneal fluid samples which after centrifugation had a cell layer of less than 5% were used.

Concentrations of progesterone and oestradiol-17β in peritoneal fluid and plasma were estimated by radioimmunoassay, using the method described by de Jong *et al.* (1974) and with kits provided by EIR (Wurenlingen, Switzerland) respectively The intra- and inter-assay standard deviation for these estimations were 7·4% and 11% for oestradiol-17β and 11·2% and 13·7% for progesterone.

Paired statistical analysis of the hormone data in plasma and peritoneal fluid used the Wilcoxon's rank sum test.

Statistical analysis of the hormone data in peritoneal fluid alone used the Mann–Whitney *U*-test.

Results

In the 27 cycles (12 patients with two cycles and three patients with one cycle) included in this study we found normal mid-luteal plasma progesterone levels (⩾25 nmol/l) and normal luteal phase durations (⩾12 days from the day of ovulation) (Table 1).

Culdocentesis failed to obtain peritoneal fluid on two occasions (no. 3 postovulatory sample, no. 14 pre-ovulatory sample). In six women (nos 2, 3, 4, 5, 6 and 15) ovulation occurred within 24 h after pre-ovulatory collection of peritoneal

Table 1. Hormonal data from 15 women of nine pre-ovulatory and 14 postovulatory plasma and peritoneal fluid samples

		Pre-ovulatory sampling							Postovulatory sampling						
		PF volume (ml)	Oestradiol-17β (pmol/l)			Progesterone (nmol/l)			PF volume (ml)	Oestradiol-17β (pmol/l)			Progesterone (nmol/l)		
Patient no	Diagnosis		PF	Plasma	Ratio	PF	Plasma	Ratio		PF	Plasma	Ratio	PF	Plasma	Ratio
1	P	8	2010	1276	1·6	6·0	2·8	2·1	8	3927	157	25·0	551	12·6	43·8
2	P	4	732	763	1·0	2·1	1·8	1·2	4	750	430	1·7	28	12·6	2·2
3	P	7·5	2028	552	3·7	14·1	3·5	4·0							
4	U	12	1401	1325	1·1	6·8	3·2	2·1	18	1398	404	3·5	14	3·0	5·0
5	U	11	1072	945	1·1	7·9	3·3	2·4	35	981	269	3·6	166	8·5	19·6
6	U	4	172	669	0·3	4·7	4·8	1·0	30	288	305	0·9	168	12·2	13·8
7	U	3	325	755	0·4	4·6	3·2	1·4	4	3333	161	20·7	713	10·2	70·0
8	U								15	498	791	0·6	5	5·0	1·1
9	U								15	6534	666	10·8	2225	17.3	128·6
10	U								8	1269	396	3·2	154	9·6	16·1
11	U								7	3507	142	24·7	586	3·4	172·3
12	E	5	477	384	1·2	5·1	4·0	1·3	10	4341	207	21·0	370	8·2	45·2
13	E								13	3132	350	8·9	578	5·7	101·5
14	E								7	3387	193	17·6	687	11·6	59·2
15	E	3·5	383	803	0·5	5·3	4·5	1·2	8	621	293	2·2	278	7·5	37·1

PF, Peritoneal fluid

P, Proven fertility, U, unexplained infertility, E, endometriosis

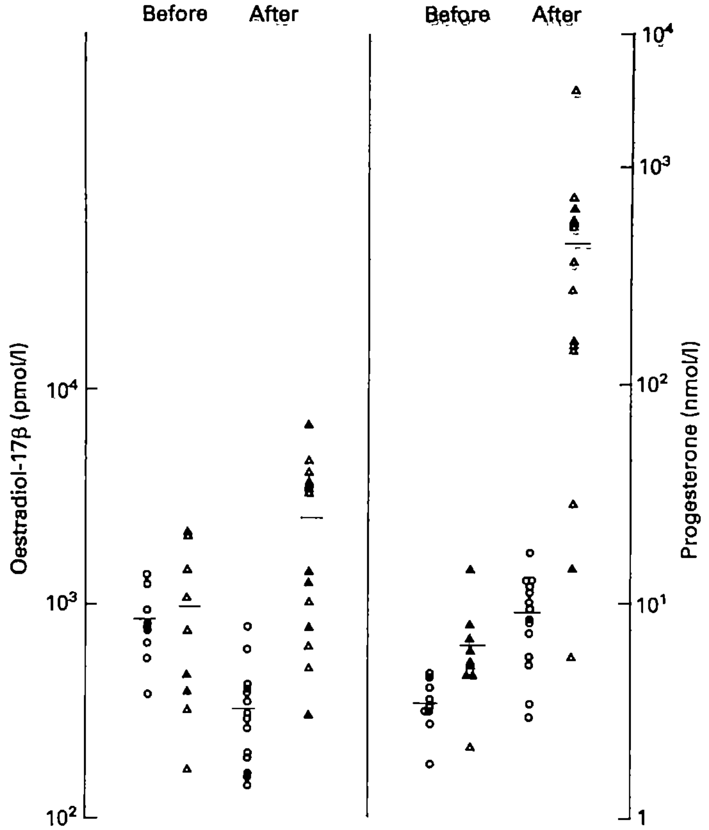

Fig. 1. Oestradiol-17β and progesterone levels in plasma (○) and peritoneal fluid (△) on a log scale Horizontal lines represent the mean concentration

fluid and in three women (nos 1, 7 and 12) within 24–48 h.

In five women (nos 8, 9, 10, 11 and 13) no pre-ovulatory peritoneal fluid sample was collected, because ovulation had already occurred 0–24 h before the puncture procedure.

In all, nine pre-ovulatory and 14 postovulatory peritoneal fluid and plasma samples were available for further analysis.

In three women (nos 2, 4 and 8) a cystic luteal structure was observed by ultrasound at the time of postovulatory culdocentesis. The mean diameter of this echo-free structure was nearly equal to that of the pre-ovulatory follicle although before this observation there had been an ovulation according to our standards (a reduction of the follicular mean diameter of at least 5 mm).

Comparison of steroid hormone levels in plasma and peritoneal fluid

Before ovulation (nine cycles) there was no significant difference between the mean oestradiol-17β level in plasma (830 pmol/l, range 384–1325 pmol/l) and peritoneal fluid (956 pmol/l, range 172–2028 pmol/l), the peritoneal fluid/plasma ratio of oestradiol-17β was 1·2 (range 0·3–3·7) (Fig. 1).

After ovulation (14 cycles) the mean oestradiol-17β level in plasma (336 pmol/l, range 142–791 pmol/l) was significantly lower ($P<0{\cdot}01$) than that in peritoneal fluid (2426 pmol/l, range 288–6534 pmol/l), the mean peritoneal fluid/plasma ratio of oestradiol-17β was 10·3 (range 0·6–25·0).

Before ovulation (nine cycles) the mean progesterone level in peritoneal fluid (6·3 nmol/l, range 2·1–14·1 nmol/l) was significantly higher ($P<0{\cdot}02$) than that in plasma (3·5 nmol/l, range 1·8–4·8 nmol/l), the mean peritoneal fluid/plasma ratio of progesterone was 1·9 (range 1·0–4·0).

After ovulation (14 cycles) this difference in mean progesterone level between peritoneal fluid (466·4 nmol/l, range 5–2225 nmol/l) and plasma (9·1 nmol/l, range 3·0–17·3 nmol/l) became much more pronounced ($P<0{\cdot}01$), the mean peritoneal fluid/plasma ratio of progesterone being 51·1 (range 1·1–172·3).

Comparison of steroid hormone levels in peritoneal fluid

There was a wide distribution of individual oestradiol-17β values before as well as after ovulation with an overlap between both groups of values (before ovulation: 172–2028 pmol/l; after ovulation: 288–6534 pmol/l)(Fig. 1). There was no statistically significant difference between the mean pre- and post-ovulatory oestradiol-17β level in peritoneal fluid.

The mean peritoneal fluid progesterone level was significantly higher after ovulation ($P<0·01$) than that before ovulation. Before ovulation, progesterone levels in peritoneal fluid were low (<15 nmol/l) whereas after ovulation there was a wide distribution of individual values (5·3–2225·6 nmol/l).

Discussion

Our data relating mean oestradiol-17β and progesterone levels in plasma and peritoneal fluid shortly before and after ovulation are in agreement with previous reports (Maathuis *et al.* 1978; Donnez *et al.* 1982; Zorn *et al* 1982). Before ovulation the mean oestradiol-17β levels in plasma and peritoneal fluid are not essentially different, whereas the progesterone level in peritoneal fluid is significantly higher than that in plasma. After ovulation both the mean oestradiol-17β and progesterone levels in peritoneal fluid are significantly higher than the values in plasma, with the mean ratio between peritoneal fluid and plasma being 10·3 for oestradiol-17β and 51·1 for progesterone.

A marked increase in the mean progesterone level in peritoneal fluid after ovulation has been reported (Maathuis *et al.* 1978; Donnez *et al.* 1982; Zorn *et al.* 1982) and this was confirmed in the present study. The three women with relatively low postovulatory progesterone levels (nos 2, 4 and 8), resulting in a small overlap with the pre-ovulatory values, each, by ultrasound, had a luteal structure with nearly the same diameter as the pre-ovulatory follicle at the time of the culdocentesis. In these women, after ovulation, there may have been re-epithelialization of the stigma so that leakage of fluid (with a high progesterone concentration) was minimal (Portuondo *et al* 1981) The secretions of the early corpus luteum, which are usually directed towards the peritoneal cavity (Donnez *et al.* 1982) are retained and result in the follicle-like structure which can be observed by ultrasound.

In a similar study, Zorn *et al.* (1982), did not observe such low postovulatory progesterone levels in peritoneal fluid. Also in contrast to Zorn *et al.* (1982), we found no significant difference between the mean oestradiol-17β levels in peritoneal fluid before and after ovulation. The explanation for these differences could be twofold: first, Zorn *et al.* (1982) detected ovulation by the relatively unreliable method of laparoscopic demonstration of the ovulation stigma and second, in both studies a limited number of pre- and post-ovulatory peritoneal fluid samples was examined

In two subjects (nos 1 and 2), we were able to compare pre- and post-ovulatory peritoneal fluid samples obtained during the same cycle. This has been described only once before by Bernardus *et al* (1983), who compared peritoneal fluid samples obtained from one patient before and after mechanical rupture of a luteinized unruptured follicle at laparoscopy; after rupture there was a marked rise in oestradiol-17β and progesterone levels resulting in much higher peritoneal fluid to plasma ratios for both hormones. In the present study, in one subject (no 1) both the oestradiol-17β and progesterone ratio in peritoneal fluid to plasma also showed a marked rise (1·6 to 25·0 and 2·1 to 43·8, respectively). In the other subject (no 2), however, both ratios remained low after ovulation (1·0 to 1·7 and 1·2 to 2·2, respectively), and this was associated with the development of a cystic luteal structure.

The detection of ovulation or of the unruptured luteinized follicle by steroid hormone assays of peritoneal fluid is based on differences in hormone levels before and after ovulation. We conclude that oestradiol-17β determination is of limited value, since both pre- and post-ovulatory values show a wide distribution. More consistent changes are seen in peritoneal fluid progesterone concentrations before and after ovulation. However, low postovulatory peritoneal fluid progesterone levels may result from reduced leakage of fluid from the ovulation stigma.

Acknowledgments

We are grateful to Mrs Evelien Cappon and Mrs Monica Vervoort for performing the oestradiol-

17β and progesterone estimations and to Pie-Data Medicals, The Netherlands, for providing the Pie-Data Medical Scanner 900 for this study, and to Sylvia Noordzij for typing out this manuscript.

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Received 5 February 1986
Accepted 8 July 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 554–558

Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid

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Summary. Thirty-five patients with menorrhagia were treated in a double-blind crossover study with naproxen sodium and mefenamic acid after measurement of their blood loss during control menstrual cycles. Treatment with these compounds reduced the excessive bleeding by an average of 46 and 47% respectively. Drugs in the prostaglandin synthetase inhibitor group are considered to have an important place in the treatment of menorrhagia.

The social impact of menorrhagia is probably most noticeable in countries with a large female work force in paid employment, and in some societies 40% of women will undergo hysterectomy (Selwood & Wood 1978). Major surgery is undergone on the basis of subjective impressions. Renewed interest in menorrhagia and its treatment has followed the development of methods for accurate measurements of the menstrual blood loss (Hallberg & Nilsson 1964) and subjective impressions have been shown to bear little relation to measured loss (Chimbira *et al.* 1980; Fraser *et al.* 1981). Anderson *et al.* (1976) first showed that mefenamic acid could decrease menstrual blood loss in menorrhagia and this compound has led to improved tolerance of menorrhagia associated with an intrauterine contraceptive device (Guillebaud *et al.* 1978). We describe here the first comparative study of two members of the cyclo-oxygenase inhibitor group of drugs, naproxen sodium and mefenamic acid on menorrhagic blood loss.

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Patients and methods

Protocol entry criteria

The study included 50 women aged between 18 years and the menopause who were described as having ‘dysfunctional uterine bleeding’ after pelvic inflammation, fibroids or other local disease were excluded. Women with gross cycle irregularities were excluded from the study. Blood loss of 80 ml or more was confirmed during two initial control cycles. Patients taking non-steroidal anti-inflammatory drugs, steroids, or with drug sensitivity or a disorder requiring medical care were excluded as were those with poor clinic attendance and therefore thought unlikely to follow instructions carefully.

Pretreatment investigations

Gynaecological. An experienced gynaecologist assessed women attending three out-patient clinics. The patient was admitted for examination under anaesthesia and diagnostic curettage. If cervical cytology, the operative findings and endometrial histology were normal, the patient was admitted to the study from the second cycle after operation and after informed consent had been obtained.

Haematological. At the initial visit each patient underwent full thyroid, haematological and blood coagulation investigations. This ensured that patients entering the study had results within the normal range.

Randomization and design

A double-blind crossover method compared naproxen sodium with mefenamic acid using the 'double-dummy' technique. Each patient was studied for a total of six cycles. Baseline values were determined by measuring two pretreatment controlled menstruations. Two treatment order groups were defined. Group 1 = naproxen sodium in the first phase; mefenamic acid in the second phase. Group 2 = mefenamic acid in the first phase; naproxen sodium in the second phase. The treatment order group was then randomly allocated to each patient number using Fisher and Yates' Tables of random numbers. The randomization was balanced in blocks of 10. The study was approved by the District ethics committee.

Drug regimens

The naproxen sodium treatment cycle consisted of an initial loading dose of 550 mg followed by 275 mg every 6 h for 5 days— a daily total dose of 1100 mg after the first day. Mefenamic acid 500 mg was taken every 8 h—total dose 1500 mg. Compliance was assessed by patient diary cards and by return of unused medication. Using these criteria all patients were found to be compliant with taking their study medication.

Clinical assessment of response

An experienced gynaecologist assessed each patient. At the initial visit specified questions were asked relating to recent duration and volume of menstrual flow, together with associated symptoms. First, second and third follow-up assessments took place after control cycles, first treatment phase, and at the end of the study when the second treatment phase was complete.

Specified questions were again asked to establish the benefits and any side-effects of the drugs, and to obtain patient and doctor preferences. Subjective impressions were obtained from diary cards, one for each menstrual cycle, which were collected at each of the three follow-up visits. Data on amount of medication consumed, napkins or tampons soiled, and the nature of bleeding were included.

Laboratory techniques

The menstrual loss was measured using the alkaline haematin method of Hallberg & Nilsson (1964) with slight modification to accommodate the bulky material.

Statistical methods

The Mann–Whitney U-test was used to examine for differences between the groups studied and for carry-over effects. The Wilcoxon matched-pairs signed-rank test was used to test for differences from baseline and between treatments.

Results

Fifty patients were assessed during the baseline menstrual cycles but nine of these patients were withdrawn for various reasons before receiving treatment (excessive bleeding (1), personal reasons (2), insufficient menstrual loss (4), menopause (1) and abnormal coagulation tests (1)). One patients was withdrawn from the study during the first treatment phase due to excessive bleeding and she was found to have a fibroid on hysterectomy. This patient was excluded from the efficacy analysis. Five patients had <80 ml blood loss during the control menstrual cycles and although they received study medication, these patients were also excluded from the efficacy analysis and their results were examined separately.

Table 1 shows the age, duration of menorrhagia, duration of menstruation, haemoglobin and serum iron concentration at baseline for group I and group II patients. No statistically significant differences were found between the two groups at baseline.

Thirty-five patients were included in the efficacy analysis, although one patient in group II withdrew for personal reasons during the second treatment phase. Table 2 summarizes the effect of the drugs on the blood loss of menorrhagic women. The median losses for the baseline menstrual cycles in the two groups were 118·5 and 129·3 ml and confirmed the severe nature of the bleeding, but a wide range of volumes was seen, not only between patients, but in the same patient from cycle to cycle. Carry-over effects were tested for but not found ($P = 0{\cdot}96$). The average reductions in loss with mefenamic acid were 54 ml in group I and 61 ml in group II.

The respective reductions in loss with

Table 1. Clinical characteristics of study groups

Characteristic	Group I (N–M)			Group II (M–N)			
	n	Mean	(SD)	*n*	Mean	(SD)	P^*
Age (years)	19	40·5	(3.6)	19	38·1	(4·7)	0.11
Duration of menorrhagia (months)	19	55·8	(53·0)	19	45·0	(41·4)	0·44
Duration of menstruation for patients with regular menstrual cycles (days)	17	8·0	(2·8)	16	6·6	(1·5)	0·19
Haemoglobin (g/dl)	19	13·0	(1·0)	19	12 1	(1·70)	0·06
Serum iron (μmol/l)	18	14·3	(5·96)	18	11·8	(7·95)	0·18

N, Naproxen sodium; M, mefenamic acid
* Mann–Whitney *U*-test.

Table 2. Menorrrhagic blood loss (ml) and the response to cyclo-oxygenase inhibitors

	Control menstrual cycles		First treatment phase				Second treatment phase			
	n	Median (Range)	*n*	Drug	Median (range)	P^{**}	*n*	Drug	Median (range)	P^{**}
Group I	18	118·5 (68–186)	18	N	67·0 (15–151)	0·001	17	M	64·5 (22–135)	0·001
Group II	18	129·3 (58–369)	17	M	68·0 (22–381)	0·001	16	N	67·3 (18–357)	0·001
Differences between groups (P^*)		0·92			0·84				0·69	

Test for carry-over: $P^* = 0{\cdot}96$
Test for difference between treatments $P^* = 0{\cdot}12$.
*Mann–Whitney *U*-test.
**Wilcoxon signed rank test.
N,Naproxen sodium; M, mefenamic acid

naproxen sodium were 52 ml and 62 ml. Both drugs were very effective in reducing losses in the treatment cycles ($P<0{\cdot}001$). In group I the mean number of days bleeding decreased from 7·2 at baseline to 6·4 with naproxen sodium and to 5·9 ($P = 0{\cdot}01$) with mefenamic acid; in group II the mean number of days bleeding fell from 6·8 to 6·0 ($P = 0{\cdot}03$) with mefenamic acid and to 5·9 ($P = 0{\cdot}004$) with naproxen sodium. Both treatments produced significant decreases in the number of tampons used. In group I the mean number of tampons fell from 31 to 23 with both naproxen sodium ($P = 0{\cdot}003$) and mefenamic acid ($P = 0{\cdot}005$) while in group II the mean number of tampons fell from 32 to 25 with both mefenamic acid ($P = 0{\cdot}017$) and naproxen sodium ($P = 0{\cdot}003$). Haemoglobin was the laboratory variable which departed most often from its normal range, with nearly a third of patients below the lower limit of the normal range.

Drug effects

Side-effects were reported by 18 patients with naproxen sodium therapy and by 15 patients during mefenamic acid therapy. All the side-effects were transient and none required the subject to be withdrawn from the study. As expected most side-effects were gastro-intestinal and were experienced by 13 patients taking naproxen sodium and six patients taking mefenamic acid. These minor ailments included nausea, diarrhoea, abdominal discomfort and anorexia. Mefenamic acid and naproxen sodium caused central nervous system symptoms in six and five patients respectively. These patients complained of light headedness, dizziness, tiredness and headache. A small number of patients in each treatment group noted weight increase, limb pain, pelvic discomfort and post-menstrual discharge. The patients' preferences were evenly divided and there were no serious side-effects.

Discussion

The comparative study of two members of the cyclo-oxygenase inhibiting group of drugs extends the observation (Anderson *et al.* 1976) that compounds of this nature are worthy of clinical consideration for the treatment of dysfunctional uterine bleeding. Furthermore, a separate analysis of five patients (not included in the efficacy analysis as their baseline loss was under 80 ml) suggested that the treatments were also very effective in reducing the loss in women having 'normal' menstruation. The baseline average of 25·0 ml decreased to 16·5 ml with naproxen sodium and to 17·4 ml with mefenamic acid, although the number of patients was too small for statistical analysis. The study failed to suggest that one drug might have an advantage over the other. Our analysis of the nature and extent of side-effects suggests that it is reasonable to propose that in clinical practice one advantage of these drugs might be in longer-term use than that advised for other compounds such as danazol which exert their effect through a different mechanism. At present, there is not widespread use of these compounds, which have the advantage of a simple schedule started with the first signs of menstruation. The relatively low cost of such a drug regimen might be considered an advantage and influence clinical decisions.

Recent studies on the control of menstruation have examined both endometrium and myometrium. Pickles *et al.* (1965) first reported high levels of prostaglandins (PG) in menstrual fluid and these substances are the main subject of current investigations. As menstruation approaches, endometrium concentrates both PGE_2 and PGF_2 (Downie *et al.* 1974).

These compounds are vasoactive but in opposite ways and it has been suggested that abnormalities in their production may relate to the excessive loss seen in dysfunctional uterine bleeding (Rees *et al.* 1984). It is probable that the myometrium predominantly produces PGI_2 (Moonen *et al.* 1985) which like PGE_2 is a vasodilator, and furthermore that myometrial PG synthesis may depend on intact endometrium supplying it with precursor endoperoxide (Cameron *et al.* 1985) The abnormal PG production in the menorrhagic uterus appears to result from an as yet undefined endometrial–myometrial interaction.

The drugs in this study might be expected to be effective in long-term use. However, clinical application of cyclo-oxygenase inhibitors, as with luteal phase progestogens, is likely to be of short duration and this relates to the very persistent nature of menorrhagia and the unattractive prospect of long-term drug treatment. An interesting aspect of the study was that the reduction in the number of tampons required each month and the patients' descriptions of reduction in bleeding appeared to be much less than that expected from the measured reduction in loss. A 'normal' curettage may not always exclude a diagnosis of small myoma or polyp and as dysfunctional menorrhagia tends to persist through the third and fourth decades of life, hysterectomy will always remain the standby for women who do not want to bear children. We believe cyclo-oxygenase inhibitors are useful for women with menorrhagia and a normal uterus and for menorrhagia associated with an intra-uterine contraceptive device.

Acknowledgments

Grateful thanks to Lisa Smart for organizational and secretarial assistance; Nigel Levinson of Syntex Pharmaceuticals Ltd; the gynaecological consultants and staff of Pembury and Sevenoaks Hospitals. Professor P. Freeman provided the statistical guidance.

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Received 19 September 1985
Resubmitted 2 May 1986
Accepted 20 January 1987

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 559–567

Effects of seven low dose combined oral contraceptives on high density lipoprotein subfractions

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Summary. The effects on lipid metabolism of seven combined oral contraceptives were investigated, particularly the effects on high density lipoprotein (HDL) subfractions, which were separated by density gradient ultracentrifugation. There were no differences between the preparations in the effects on the LDL fraction, the so-called atherogenic particle, but there were marked differences in the effects on the anti-atherogenic HDL fraction, of which the effects on HDL-2 were most pronounced. After treatment with monophasic cyproterone acetate and biphasic desogestrel, the cholesterol and phospholipid contents of the HDL-2 fraction were significantly higher than those found after treatment with the other preparations. The lowest values were found after treatment with monophasic levonorgestrel, whereas monophasic desogestrel, triphasic levonorgestrel, monophasic norethisterone and triphasic gestoden induced intermediate values for these variables. The levels of HDL-2 reflect the intrinsic androgenicity of the various progestogens used in the preparations.

During the last decade important changes have been made in the composition of oral contraceptives. First, a reduction in the dose of oestrogen was introduced because of thromboembolic complications (Royal College of General Practitioners Oral Contraceptive Study 1977) Second, the dose of progestogens was reduced, because of disturbances in metabolic pathways, which were related to an increased risk of cardiovascular diseases. This has ultimately led to the introduction of the triphasic concept (Elstein 1983). The type of progestogen has also been changed to give a more specific progestogenic compound. A few years ago desogestrel was introduced; its active metabolite, 3-keto-desogestrel shows less androgenic properties than other progestogens (Bergink *et al.* 1983). Results of epidemiological studies have shown an inverse correlation between high density lipoprotein (HDL)-cholesterol levels and the risk for cardiovascular disease (Miller *et al.* 1977; Castelli *et al.* 1977; Gordon *et al.* 1977; Goldbourt & Medalie 1979). Nowadays the HDL subfractions are considered to be better risk discriminators. Miller *et al.* (1977) found the strongest inverse relation between HDL-2 cholesterol levels and vascular score. Low density lipoprotein (LDL) is the other important lipoprotein particle; the severity of cardiovascular disease is positively correlated with LDL-cholesterol levels (Miller *et al.* 1977; Castelli *et al.* 1977; Gordon *et al.* 1977; Goldbourt & Medalie 1979).

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Table 1. Composition and intake regimen of the oral contraceptive preparations

Preparation	Days	Amount of ethinyl-oestradiol (μg)	Amount and type of the progestogen (μg)	
(1) Monophasic LNG (Microgynon)	21	30	150	Levonorgestrel
(2) Monophasic NET (Brevicon-1)	21	35	1000	Norethisterone
(3) Monophasic DSG (Marvelon)	21	30	150	Desogestrel
(4) Triphasic LNG (Logynon)	6	30	50	Levonorgestrel
	5	40	75	Levonorgestrel
	10	30	125	Levonorgestrel
(5) Monophasic CPA	21	35	2000	Cyproterone acetate
(6) Triphasic GSD	6	30	50	Gestoden
	5	40	70	Gestoden
	10	30	100	Gestoden
(7) Biphasic DSG	7	40	25	Desogestrel
	14	30	125	Desogestrel

It is well known that exogenous steroid hormones have an influence on lipid metabolism. Oestrogens increase HDL-cholesterol and triglycerides, whereas progestogens increase LDL-cholesterol and decrease HDL-cholesterol. However, the ultimate effect of synthetic progestogens depends on the dose and the intrinsic androgenic properties of the progestogens used (Oster *et al.* 1982; Knopp *et al* 1982; Plunkett 1982; Wahl *et al.* 1983).

A number of metabolic studies (Elstein 1983; Samsioe 1982; Bergink *et al.* 1982, Briggs & Briggs 1982; Cullberg *et al.* 1982; Gaspard *et al.* 1985) have shown that some oral contraceptive preparations developed recently have minor or no adverse effects on lipid metabolism. These results have come from various research centres using different methods. The aim of the present study was to compare the effects of seven low-dose oral contraceptives on lipid metabolism in one research centre. The lipid composition of the various lipoprotein fractions, including HDL-2 and HDL-3, was assessed after separation in a density gradient by ultracentrifugation. In this study the four most commonly used formulations were investigated, together with three preparations which are in a final stage of development.

Subjects and methods

Seventy healthy female volunteers were selected on the basis of the following criteria: age between 16 and 40 years, weight within 90–120% of normal body weight, good general health, no use of other medications, regular menstrual cycles (26–35 days) and no oral contraceptive use for at least 3 months preceding the study. No change in life style was permitted during the study. The women gave their written informed consent for participating in the study, which consisted of one pretreatment cycle and six treatment cycles. The women were randomly allocated to seven groups (10 volunteers per group), each group to be treated with one of the seven preparations. The composition and intake regimen of the various oral contraceptive preparations are presented in Table 1. During the luteal phase of the control cycle (days 19–24) and on day 15 or 19 of the first, third and sixth treatment cycles, blood samples were taken at 12.00–15.00 hours after patients had fasted overnight

Consent of the local ethics committee was obtained for this study

Serum or plasma preparations

Samples were prepared by standard laboratory procedures. The serum or plasma was used for the assessment of total cholesterol, total phospholipids, total triglycerides, apolipoproteins A-I and B and for the separation of the various lipoprotein fractions Cholesterol phospholipids and triglycerides were estimated by enzymatic procedures using commercially available test-kits on the CentrifiChem R System 500 or the Multistat III FLS. Apolipoprotein A-I and apolipoprotein B were determined by immuno-

Table 2. Geometric mean values adjusted for total cholesterol (nmol/l), total phospholipids (g/l) and total triglycerides (mmol/l) during treatment (mean pretreatment values were 4·11 mmol/l, 1·84 g/l and 0·75 mmol/l, respectively)

	Total cholesterol at treatment cycle			Total phospholipids at treatment cycle			Total triglycerides at treatment cycle		
Prep	1	3	6	1	3	6	1	3	6
(1)	3·89	4·14	4·16	1·83	1·96	1·92	0·89	1·06	1·03
(2)	4·25	4·49	4·18	1·99	2·15	2·00	0·98	1·17	1·01
(3)	4·36	4·55	4·33	2·04	2·09	2·16	1·12	1·11	1·20
(4)	3·97	4·12	3·95	1·96	1·97	1·96	0·89	0·96	1·06
(5)	4·40	4·61	4·61	2·11	2·22	2·35	1·14	1·64	1·73
(6)	3·89	4·22	4·08	1·91	1·99	1·99	1·13	1·36	1·32
(7)	4·19	4·47	4·42	1·99	2·13	2·15	0·93	1·25	1·19

(1) Monophasic LNG, (2) Monophasic NET; (3) Monophasic DSG; (4) Triphasic LNG, (5) Monophasic CPA, (6) Triphasic GSD; (7) Biphasic DSG

electrophoresis as described by Laurell (1966). The cholesterol content in the total HDL fraction was assessed after precipitation of apolipoprotein B-containing lipoprotein particles using the phosphotungstate method of Boehringer. Lipoprotein particles were separated from fresh frozen plasma by ultracentrifugation in a density gradient following the procedure described by Terpstra *et al.* (1981). The lipoprotein particles were stained with fat red stain to show the various lipoprotein fractions.

Statistics

The differences between the preparations in the effect on the various variables were analysed by an analysis of covariance, using the pretreatment value as the covariate and the 6-month value as the effect of the treatment. The data were log transformed to meet the requirements for normal distribution. If the overall *F*-test for differences between treatments was significant at the 0·05 level of significance for a variable, pairs of groups were anlaysed with a *t*-test at the 0·05 level of significance. In the Tables and Figures the geometric means adjusted for difference in pretreatment values are presented at the times of blood sampling.

Results

For the clarity of the discussion we put most emphasis on the effects after 6 months of treatment, because then a metabolic steady state has been achieved for the effects of the various treatments. Table 2 shows the geometric mean group values at the times of blood sampling for total cholesterol, total phospholipids and total triglycerides. No significant differences between preparations were found for effects on total cholesterol. Monophasic CPA induced significantly higher total phospholipid levels and total triglyceride levels than the other preparations except for monophasic DSG with respect to the phospholipids and for triphasic GSD with respect to the triglycerides.

The effects on total HDL-cholesterol (precipitation procedure) of the various preparations are shown in Fig. 1. Treatment with monophasic DSG (3), biphasic DSG (7), triphasic LNG (4) and monophasic CPA (5) induced significantly higher levels of HDL-cholesterol than treatment with monophasic LNG (1). Neither the differences in effects between triphasic GSD, or monophasic NET and monophasic LNG nor the differences between triphasic GSD, or monophasic NET and the other four preparations were significant

After density gradient centrifugation various lipoprotein particles can be identified. We will restrict ourselves to the lipid composition of the particles in the following variables· cholesterol content of HDL-2, HDL-3 and LDL and the phospholipid content of HDL-2 and HDL-3, since these variables are the most relevant for the development of cardiovascular disease. The geometric mean values for HDL-2 cholesterol levels in the seven treatment groups are shown in Fig 2. The values induced by treatment with monophasic CPA (5) and biphasic DSG (7) were significantly higher than with the other prep-

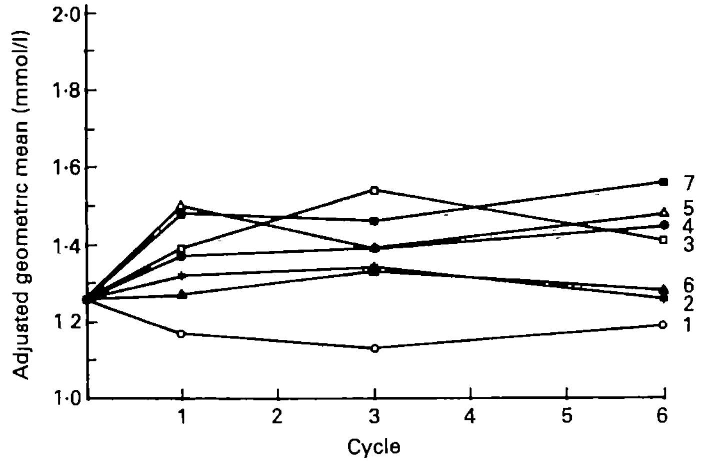

Fig. 1. Effects of monophasic LNG (prep 1; ○—○), monophasic NET (prep 2; *—*), monophasic DSG (prep 3; □---□), triphasic LNG (pre 4; ●—●), monophasic CPA (prep 5; △---△), triphasic GSD (prep 6, ▲---▲) and biphasic DSG (prep 7; ■—■) on total HDL-cholesterol (precipitation method). The adjusted mean values (corrected for differences in pretreatment values) are presented See Table 1 for composition of preparations.

arations. Monophasic DSG (3) induced higher values than those with the other four preparations, but the difference was not significant. Monophasic LNG (1), which induced the lowest total HDL-cholesterol level, was again the preparation associated with the lowest mean value for HDL-2 cholesterol level.

Figure 3 shows that the effects of the various preparations on the phospholipid content of the HDL-2 subfraction follow the same patterns as shown for the effects on HDL-2 cholesterol Monophasic CPA (5) with biphasic DSG (7) induced significantly higher values than the other five preparations. The effects of the preparations on HDL-3 cholesterol and HDL-3 phospholipids are presented in Figs 4 and 5, respectively. For both variables no significant differences between the preparations could be

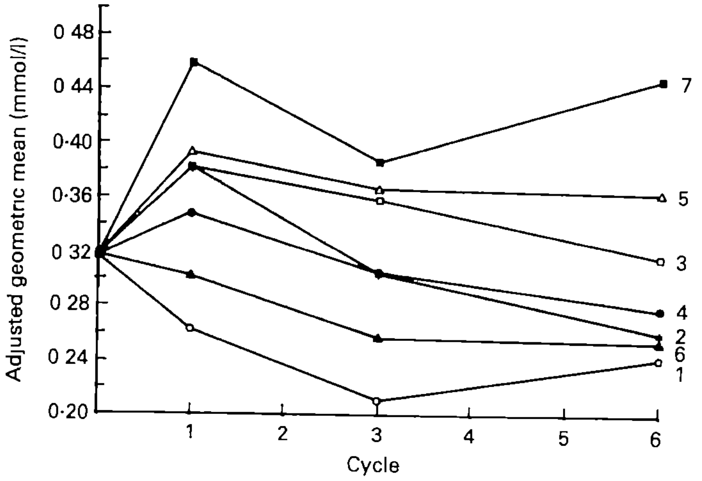

Fig. 2. Effects of the seven preparations on HDL-2 cholesterol. For explanation of the symbols see Fig 1.

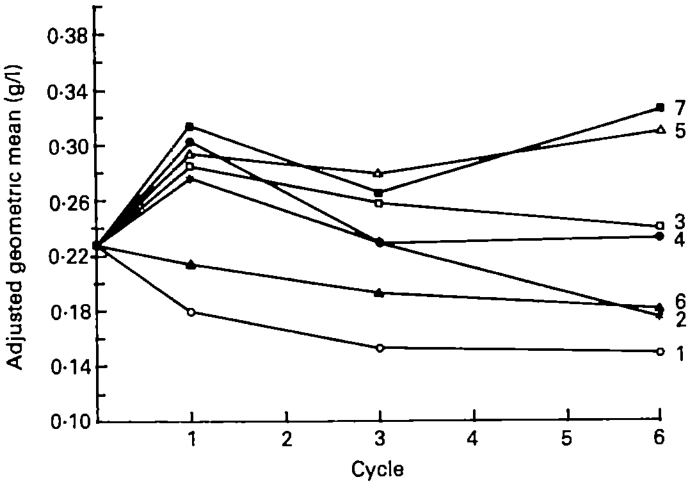

Fig. 3. Effects of the seven preparations on HDL-2 phospholipids. For explanation of the symbols see Fig 1

observed. With the exception that treatment with monophasic LNG (1) induced significantly lower values than treatment with monophasic CPA (5) or with biphasic DSG (7).

The effects of the preparations on the major apolipoprotein of HDL, namely apo A-I, are shown in Fig. 6. The apo A-I level induced by monophasic LNG (1) was significantly lower than those induced by all the other preparations. The same ranking of the preparations was found for effects on apo A-I as, was found for the effects on the other HDL-related variables.

Table 3 shows the effect of the preparations on LDL-cholesterol and apo B, the major apolipoprotein of LDL. For both variables no significant differences between the preparations were found.

Discussion

The aim of the present study was to investigate the effect of seven low dose combined oral contraceptives on lipid metabolism including HDL subfraction. At present most combined prep-

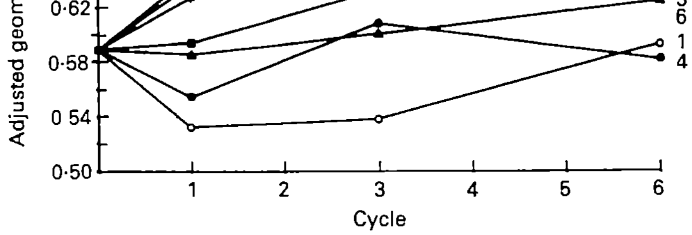

Fig. 4. Effects of the seven preparations on HDL-3 cholesterol. For explanation of the symbols see Fig. 1.

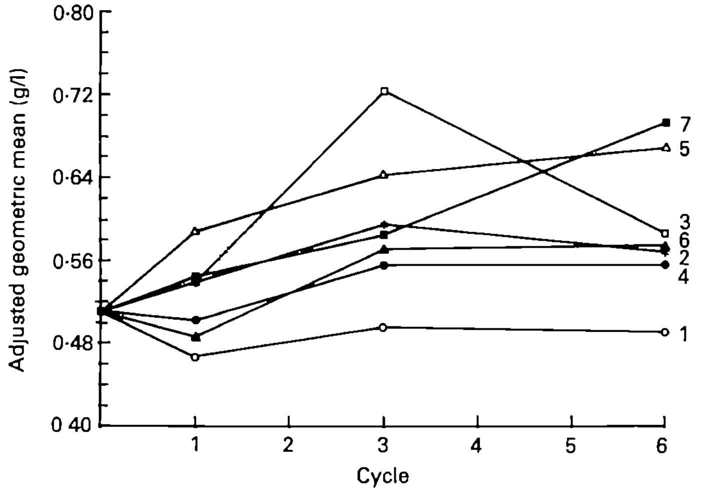

Fig. 5. Effects of the seven preparations on HDL-3 phospholipids. For explanation of the symbols see Fig 1

arations contain 30–35 µg of ethinyl oestradiol. Differences between preparations in the effects on lipid metabolism, that were found in the present study, must be attributed to the type and dose of the progestogen. Differences between preparations in effects on some lipid variables have indeed been claimed (Godsland & Wynn 1984*a*, *b*; Kuusi *et al.* 1984), but this was based on results from different research centres using different populations and methods. Until now, the attention on lipid metabolism has mainly been focused on total HDL-cholesterol, due to the proposed protective effect of this fraction on the development of cardiovascular diseases; but the effects on the HDL subfractions may be more relevant (Miller *et al.* 1981; Godsland & Wynn 1984*a*, *b*).

We used density gradient ultracentrifugation to investigate the effects of the seven preparations on HDL-2 and HDL-3 levels. The density gradient technique was chosen because this method is more reliable than the non-specific precipitation procedures. In addition to the cholesterol content of the fractions we also

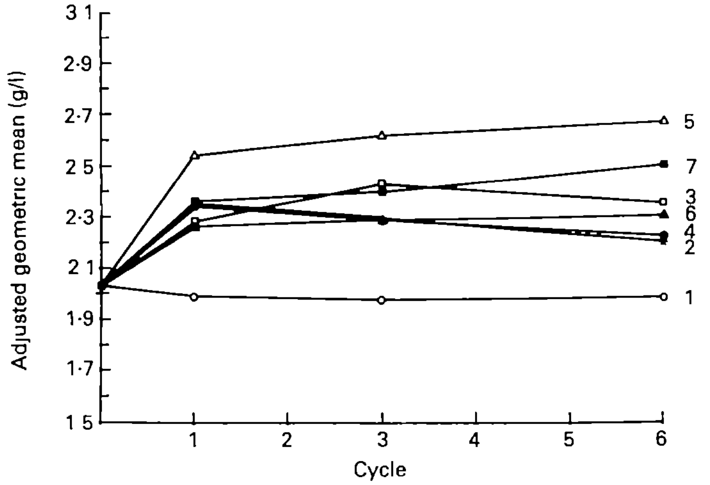

Fig. 6. Effects of the seven preparations on apolipoprotein A-I. For explanation of the symbols see Fig 1

Table 3. Geometric mean values for LDL-cholesterol (mmol/l) and apolipoprotein B (g/l) during treatment (mean pretreatment values were 1·88 mmol/l and 0·53 g/l, respectively)

	LDL-cholesterol at treatment cycle			Apolipoprotein B at treatment cycle		
Preparation	1	3	6	1	3	6
(1) Monophasic LNG	1·72	1·92	2·04	0·48	0·61	0·63
(2) Monophasic NET	1·96	2·09	1·84	0·60	0·65	0·63
(3) Monophasic DSG	2·00	1·97	1·92	0·51	0·60	0·73
(4) Triphasic LNG	1·69	1·91	1·77	0·55	0·57	0·58
(5) Monophasic CPA	1·82	1·89	1·93	0·58	0·62	0·76
(6) Triphasic GSD	1·74	2·01	1·93	0·54	0·60	0·72
(7) Biphasic DSG	1·78	1·90	1·89	0·49	0·59	0·71

measured their phospholipid content. Phospholipids form a structural part of the lipoprotein particle and are therefore an indication of the number of particles in circulation.

In this study the most profound differences between the preparations were found in the effects on the HDL components. The highest values for total HDL-cholesterol, apo A-I, HDL-2 cholesterol, HDL-2 phospholipids, HDL-3 cholesterol and HDL-3 phospholipids were consistently found in the groups treated with monophasic CPA and biphasic DSG, whereas the lowest values were found in the groups treated with monophasic LNG. Treatment with monophasic DSG triphasic LNG, monophasic NET, and triphasic GSD produced intermediate values for these variables. We may therefore conclude that oral contraceptive preparations do differ in their effects on HDL-related variables, the levels of which have been shown to correlate inversely with the severity of cardiovascular diseases (Miller *et al.* 1977; Castelli *et al.* 1977; Gordon *et al.* 1977; Goldbourt & Medalie 1979). The differences in the effects on lipid metabolism between the preparations used in the present study are due to the type and dose of the progestogen. Except for cyproterone acetate, which is a pregnane derivative, the other progestogens are derived from 19-nortestosterone and these compounds have intrinsic androgenic activity Receptor binding studies have shown that the affinity for the androgen receptor varies between different progestogens. The following ranking (high to low) of the intrinsic androgenicity of the progestogens has been found: levonorgestrel ≥ gestoden > norethisterone = 3-keto-desogestrel (the active metabolite of desogestrel) ≫ cyproterone acetate (Bergink *et al.* 1983; Bergink & Kloosterboer 1985). Concerning binding to the progesterone receptor the ranking (high to low) is: gestoden > 3-keto desogestrel > levonorgestrel > norethisterone > cyproterone acetate.

Tikkanen *et al.* (1981*a*, *b*, 1982) found that progestogens with intrinsic androgenicity induce lower HDL levels, because of stimulation of the hepatic lipase activity. This enzyme is responsible for the catabolism of the HDL-2 subfraction and the activity is stimulated by androgens and decreased by oestrogen. The ultimate effect of a combined oral contraceptive on hepatic lipase, and consequently its effect on HDL-2, will be determined by the hormonal composition of the preparations. The dose and type of the progestogen are decisive for the effects of the various preparations in this study, because all contain the same amount of ethinyl oestradiol. The influence of the type of the progestogen can best be observed when the same amount of progestogen is taken during the cycle in the same regimen. This is the case when monophasic DSG and monophasic LNG are compared. Our results show that monophasic DSG has induced higher HDL-2 levels (cholesterol and phospholipids) than has monophasic LNG.

Kuusi *et al.* (1985) found indeed a lower hepatic lipase activity in women receiving desogestrel alone than in those receiving levonorgestrel, this was considered to be due to the lower androgenicity of desogestrel. These findings are confirmed in the present study. Reduction in dosage of levonorgestrel in the triphasic preparation and of desogestrel in the biphasic concept induced higher HDL-2 levels than treatment with the monophasic preparations of levonorgestrel and desogestrel respectively The biphasic DSG preparation induced the highest

HDL-2 values of all preparations. Apparently the effect of ethinyloestradiol on HDL-2 was hardly affected by the low amount of desogestrel in this preparation. Thus dose reduction leads to a lower androgenicity of the preparations and consequently to higher HDL-2 levels most likely via a reduction in the hepatic lipase activity. We were surprised to find in this study that treatment with gestoden, a potent progestogen with the same androgenic activity as levonorgestrel, when given in the triphasic concept in a slightly lower dosage than triphasic LNG induced lower HDL-2 values than triphasic LNG. Probably the stimulation of the hepatic lipase activity is higher than expected on basis of the androgen receptor binding activity. The two weak progestogens, cyproterone acetate and norethisterone, differ considerably in their androgenic properties. Cyproterone acetate has hardly, if any, intrinsic androgen activity and the effect ethinyl oestradiol on HDL is hardly opposed. In comparison with the other preparations, monophasic CPA and biphasic DSG induced the highest HDL-2 levels. Monophasic NET induced far lower HDL-2 levels than did monophasic CPA, which can best be explained by the difference in androgenicity between the two progestogens. HDL-3 levels are thought to be less relevant for the development of cardiovascular disease. A number of studies have shown that this fraction is less influenced by exogenous factors, including hormones. Although we could not show any statistically significant differences between the preparations in effects on the HDL-3 fraction, there was considerable variation and the values did not appear to be as constant as reported in other studies (Tikkanen *et al.* 1981*a, b,* 1982; Kuusi *et al.* 1985). In conclusion we found marked differences between oral contraceptive preparations in effects on the level of the HDL-2 fraction, which has been shown by Miller *et al.* (1981) to correlate inversely with a cardiovascular score. Whether a higher HDL-2 level (based on cholesterol and phospholipids) induced by some oral contraceptives could offer some protection against the development of cardiovascular disease is uncertain because the disease is determined by several factors and not by lipids alone.

Acknowledgments

This study was supported by Cilag, Organon, Schering and Wyeth (The Netherlands).

The contribution of Miss M. Zwinkels to the organization of this study is greatly appreciated. The authors are indebted to Dr F. J. Verbon for performing the statistical analysis. They thank Mrs M. G. J. A. Heymans- v. Zutven for skilful technical assistance, Dr H. D. Berkeley for critical reading of the manuscript and Miss H. G. F. Roodvoets for preparation of the manuscript.

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Received 19 March 1986
Accepted 7 October 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol 94, pp. 568–574

Treatment with oral piperazine oestrone sulphate for genuine stress incontinence in postmenopausal women

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Summary. The use of oestrogens in the treatment of genuine stress incontinence was assessed by a double-blind prospective trial in 36 postmenopausal women with genuine stress incontinence who received 3 months of cyclical treatment with either piperazine oestrone sulphate or a matching placebo. Patients were assessed subjectively and objectively before and after treatment by 7-day bladder charts, urethral pressure profiles (UPP), the Urilos nappy test, vaginal cytology and hormone assays (plasma oestrogens and gonadotrophins). There was no statistical difference in the subjective response to treatment between the two groups. After 6 weeks of treatment there was a greater reduction in the number of pad changes/24 h in the oestrogen-treated patients that approached statistical significance but, because of a marked response in the placebo group, this difference was not significant after 3 months of treatment. There were also no significant differences between the two groups with respect to the UPP or Urilos measurements but the vaginal cytology and hormone profiles were significantly affected by oestrogens. In view of the possible risks of oestrogen therapy its use in genuine stress incontinence is limited.

The female lower urinary and genital tracts have similar embryological origins both arising from the primitive urogenital sinus (Hamilton & Mossman 1972). It is not surprising therefore that animal (Zuckerman 1940) and human cytohormonal studies (Smith 1972) indicate that the urethra appears to be sensitive to oestrogens, and oestrogen receptors have been identified predominantly in the middle and distal thirds of the human female urethra providing objective evidence that the urethra is an oestrogen 'target' organ (Iosif *et al* 1981; Wilson *et al.* 1984). Oestrogen deficiency leads to atrophy of the urethral mucosa (Smith 1972) and is believed to be a contributory factor in genuine stress incontinence (Hald 1975; Stanton 1977)

The use of oestrogen therapy for genuine stress incontinence is, however, controversial. Most studies which have indicated that oestrogens are helpful were based only on a subjective assessment of results (Salmon *et al.* 1941; Musiani 1972). Other objective but uncontrolled studies have shown increased maximum urethral pressures (Caine & Raz 1973) and

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increased transmission of intra-abdominal pressure to the urethra with high doses of oestrogen given orally (Rud 1980) and intravaginally (Hilton and Stanton 1983). In a double-blind trial Walter *et al.* (1978) noted a significant reduction in frequency and urgency with oestrogens, but no changes in either stress incontinence or the urethral pressure profiles.

The purpose of this prospective double-blind trial was to assess objectively the effects of oral oestrogen therapy in postmenopausal patients with genuine stress incontinence

Patients and methods

The study comprised 36 patients aged 47–72 (mean 57·2) years; 30 of them had had a natural menopause between 1 to 24 (mean 10·1) years previously and six had had a hysterectomy All the patients had serum gonadotrophin concentrations in the postmenopausal range (Jacobs & Murray 1976). All had genuine stress incontinence and stable detrusor function diagnosed using synchronous video pressure flow cystourethrography (Bates & Corney 1971) Outflow obstruction was excluded using independent flowmetry (Tanmen 1973).

No patient had received hormone treatment in the preceding 3 months and there were no contra-indications to oestrogen therapy. Each patient had a full clinical examination before the study including screening for breast and genital cancer; weight and blood pressure were recorded. All patients had negative urine cultures before, during and after treatment.

The trial design was a double-blind comparative study. Each patient was randomly assigned to receive 3 months of treatment with either piperazine oestrone sulphate (Harmogen) (2 × 1·5 mg tablets taken at night) in 3-week courses with one treatment-free week between each course or a matching placebo (2 tablets taken at night) taken in an identical manner. The method of random allocation was that given by standard statistical tables for random allocation of two drugs. The placebo tablets were composed of lactose, dye, acacia powder, maize starch, talc and stearic acid. The study had the approval of the hospital ethics committee and all patients gave informed consent.

Subjective assessment

Subjective assessment was made at 6 weeks and at the last week of treatment (week 11) when the patients were asked if they were much improved, improved or no better. The patients in both groups who responded to therapy (i.e. the first two categories) were further assessed at 6 and 12 weeks after the tablets were discontinued.

Objective assessment

Seven-day bladder charts (Wilson *et al* 1980). The number of micturitions and pad/pant changes per 24 h were recorded for the week before the start of treatment (week −1), for the first, sixth and last weeks of treatment (week 11). Those patients who responded to therapy also completed a bladder chart, 6 and 12 weeks after the tablets were discontinued.

Urilos nappy test. This test, recording urine loss by an electronic quantitative measuring device for 2 h of normal activity (Wilson *et al.* 1980), was performed in 22 patients before the start and on completion of the 3-month course of treatment.

Urethral pressure profile. The method described by Brown & Wickham (1969) was used and measurements were recorded before the start and on completion of the 3-month course of treatment. The bladder was filled with 150 ml and the mean value of three consecutive profiles was recorded.

Vaginal cytology. Lateral vaginal wall smears were taken from the middle third of the vagina using saline moistened cotton tipped swabs before the start, at the sixth, and during the final week of therapy. All specimens were examined by the same cytologist and 50 cells were examined in each smear using the random counting method described by Frost (1974). The proportion of oestrogenized superficial cells to intermediate and parabasal cells was determined and expressed as a percentage of the total cell count to give the karyopyknotic index (KI). The differential count was also converted to a modified 'maturation value' (Miesels 1967) by multiplying the percentage of the various cell types by varying factors (1·0 for superficial cells, 0·6 for large intermediate cells, 0·5 for small intermediate cells and 0 for parabasal cells) and summing the products.

Hormone estimations. Venous blood was taken from 25 patients in the morning before the start of therapy and after 6 and 11 weeks of treatment, on the 20th or the 21st day of the last cycle. Oestrone and oestradiol levels were measured on ether extracts of serum by radioimmunoassay. The steroids were assayed after partition chromatography on celite columns (Large & Anderson 1979) ensuring complete specificity for each steroid. Serum follicle stimulating hormone (FSH) and serum luteinizing hormone (LH) were determined by radioimmunoassay based upon the recommended procedures of the Supraregional Assay Service for Gonadotrophins which were kindly made available by Professor S. L. Jeffcoate of the Chelsea Hospital for Women, United Kingdom.

Statistical analysis

The demographic data for the two patient groups were compared using the two-sample Student's *t*-test, Mann–Whitney *U*-test and Fisher's exact test. The results of treatment were compared using a standard analysis of variance.

Methods, definitions and units conform to the standards proposed by the International Continence Society (Bates *et al.* 1979).

Results

Of the 36 patients recruited to the study, 18 were treated with oestrogen and 18 with placebo. Two patients in the oestrogen group failed to complete the study so the statistical analysis was restricted to 16 patients in the oestrogen group and 18 in the placebo group.

The mean ages and years since the menopause were 57 and 8 for the oestrogen-treated patients and 58 and 8 for the placebo-treated patients. The two groups were also comparable with respect to height, weight, parity, duration of symptoms, grade of incontinence (Whiteside 1973) and occurrence of previous surgery for incontinence.

Subjective assessment

Seven of the 16 oestrogen-treated patients were much improved, five were improved and four were no better after treatment. Five of the 18 placebo-treated patients were much improved, five were improved and eight no better. The differences between the two treated groups were not statistically significant ($P<0{\cdot}40$).

Side-effects

Two patients in the oestrogen group failed to complete the study and were excluded from the analysis. One complained of palpitations and trembling 5 days after starting treatment and the other suffered a posterior subendocardial infarct during a serious argument 5 weeks after the start of the study. Other minor symptoms such as leg pain, breast discomfort, chest pain and nausea were uncommon and not significantly increased on oestrogen therapy.

Number of micturitions and pad changes per day

The frequency of micturition was reduced in both groups. Although the mean reduction in the oestrogen group (1·6/24 h was greater than that in the placebo group (0·3/24 h) this difference between the groups was not statistically significant (Table 1).

The number of pad changes per 24 h was reduced in both groups. After 6 weeks of treatment the mean reduction in the oestrogen group (1·6 pad changes/24 h) was greater than that in the placebo group (0·6 pad changes/24 h) and this difference approached statistical significance [$F(3{\cdot}94) = 2{\cdot}614, P = 0{\cdot}056$]. However, at the end of 3 months of treatment the mean reduction in the oestrogen group (1·5 pads/24 h) was not significantly different from that in the placebo (0.9 pads/24 h) (Table 1).

Twelve women in the oestrogen group and 10 in the placebo group were judged to have 'responded' to therapy based on their subjective assessment and bladder charts. These 22 patients attended for follow-up at 6 and 12 weeks after the end of treatment. An analysis of the 22 responders (Table 1) showed no difference between the two treatment groups for either variable frequency of micturitions [$F\ (5{\cdot}94) = 0{\cdot}430$, $P = 0{\cdot}827$] or for numbers of pad changes/24 h [$F\ (5{\cdot}95) = 1{\cdot}407$, $P = 0{\cdot}229$]. However, it did show that the improvements obtained with both oestrogen and placebo were maintained for at least 3 months after treatment.

Urethral pressure profiles

The results of the changes in the maximum urethral closure pressure (MUCP) before and after treatment are shown in Table 2. The MUCP fell slightly in both treatment groups but

Table 1. Effects of oestrogen and placebo treatment on the frequency of micturition and pad changes per day

Week of treatment	No. of micturitions/day		No. of pad changes/day	
	Oestrogen	Placebo	Oestrogen	Placebo
(a) All patients ($n = 34$)				
−1*	10·0	10·7	2·5	2·6
	(8·6–11·5)	(9·3–12·2)	(1·5–3·8)	(1·6–3·9)
1	9·1	10·4	1·3	2·2
	(7·7–10·5)	(9·1–11·9)	(0·6–2·2)	(1·3–3·3)
6	8·6	10·0	0·9	2·0
	(9·3–10·1)	(8·7–11·4)	(0·3–1·7)	(1·1–3·1)†
11	8·4	10·4	1·0	1·7
	(7·1–9·8)	(9·0–11·9)	(0·4–1·9)	(1·0–2·8)
(b) 'Responders' only ($n = 22$)				
−1	9·9	10·5	2·5	2·6
	(8·5–11·4)	(8·9–12·2)	(1·1–4·5)	(1·3–4·3)
1	8·7	10·3	1·0	1·9
	(7·4–10·1)	(8 7–12·0)	(0·2–2·3)	(0·8–3·4)
6	8·0	9·3	0·6	1 7
	(6·8–9·4)	(7·8–10·9)	(0·1–1·8)	(0·7–3·2)
11	7·9	9·1	0·6	1·0
	(6·7–9·2)	(7·7–10·8)	(0·1–1·7)	(0·3–2·2)
17	7·8	8·8	0·4	1·3
	(6·6–9·2)	(7·3–10·4)	(0–1·4)	(0·4–2·6)
23	8·1	9·2	0·6	1·2
	(6·8–9·5)	(7·7–10·8)	(0·1–1·7)	(0·4–2·5)

Results are means (95% confidence limit).
* Week −1, 7 days preceding treatment
† $0{\cdot}10 > P > 0{\cdot}05$.

the differences were not statistically significant [F (1·29) = 0·011, P = 0·915]. The effect of oestrogen on MUCP was not significantly different from that of placebo.

The functional and anatomical urethral lengths were virtually unchanged after treatment in both groups.

Urilos nappy test

The results of the Urilos nappy test before and after treatment in 22 women (8 in the oestrogen group, 14 in the placebo group) are shown in Table 2. The changes with treatment were not significantly different between the two groups.

Vaginal cytology

At the start of therapy both groups had a mean KI value of 2 but at the completion of therapy the KI was significantly higher in the oestrogen group (mean 20, 95% confidence limit 12–35) than in the placebo group (mean 3, 95% con-

Table 2. Maximum urethral closure pressure (MUCP) and Urilos test results before and after oestrogen or placebo therapy

Week of treatment	MUCP (cm H_2O)		Urine loss (Urilos) (ml/2 h activity)	
	Oestrogen ($n = 16$)	Placebo ($n = 18$)	Oestrogen ($n = 8$)	Placebo ($n = 14$)
0	57 (51–62)	53 (49–58)	5 (0–13)	5 (0–12)
11	53 (48–58)	50 (46–55)	6 (0–14)	3 (0–10)

Results are means (95% confidence limit).

fidence limit 1–6) ($P<0\cdot01$). Similar results were found for the mean maturation values, these were 33·8 and 37·8 before treatment in the oestrogen and placebo groups, respectively; at week 11 the mean maturation values were 69·7 (95% confidence limit 61·8–77·5) in the oestrogen group and 39·9 (95% confidence limit 32·5–47·2) in the placebo group, this difference between the groups was statistically significant ($P<0\cdot01$).

Hormone assays

The mean FSH level was significantly reduced in the oestrogen group but unaltered in the placebo group. Before treatment the mean FSH levels were 87 and 84 i.u./l in the oestrogen and placebo group, respectively; at week 11 the mean FSH levels were 54 i.u./l (95% confidence limit 40–68) in the oestogen group and 80 (95% confidence limit 67–93) in the placebo group; the difference was significant ($P<0\cdot01$). The effect of oestrogen on LH levels was not significantly different from that of placebo. The serum oestradiol levels were significantly increased by oestrogen but unchanged by placebo. Before therapy the mean oestradiol levels were 82 and 83 pmol/l in the oestrogen and placebo groups, respectively, and at the completion of therapy, the mean oestradiol levels were 409 pmol/l (95% confidence limit 255–655) in the oestrogen group and 90 pmol/l (95% confidence limit 57–141) in the placebo group ($P<0\cdot01$). Similar results were obtained for mean oestrone values which were in the oestrogen and placebo groups, respectively, 137 and 241 pmol/l at the start of treatment and 1341 pmol/l (95% confidence limit 729–2463) and 203 pmol/l (95% confidence limit 113–363) at 11 weeks, the difference between the two groups was statistically significant ($P<0\cdot01$).

Discussion

The therapeutic benefits of oral oestrogen therapy in women with genuine stress incontinence included a reduction in the mean number of pad changes per day that approached statistical significance when compared with the reduction in the placebo group. However, by the time the 3 months of treatment was completed, there was no significant difference between the two groups due to a definite response in the placebo group. The improvement in the number of pads required per day was maintained equally by both groups for 3 months after the cessation of therapy.

With any medication the benefits of treatment have to be weighed against the risks and adverse side-effects. Although the occurrence of side-effects in our study was similar for both groups, oestrogen therapy entails definite risks. Complications of unopposed oestrogen treatment are not clearly known but may include endometrial and breast cancer, hypertension, hyperlipidaemia and gall-bladder disease (Judd 1983). The benefits of oestrogen therapy in genuine stress incontinence have to be weighed against these possible risks, and although these will vary between women, our results indicate that the therapeutic value of oestrogen in this condition is limited. In this trial, unopposed oestrogens were given cyclically to ensure that the double-blind nature of the study was maintained. Unopposed oestrogens are associated (in approximately 30% of patients) with both cystic glandular and atypical endometrial hyperplasia (Whitehead *et al.* 1978) and the addition of a progestogen for 7–12 days each month has been recommended to protect against the endometrial hyperstimulation induced by oestrogen (Whitehead *et al.* 1978) Although no progestogen receptors have been identified in the urethra (Wilson *et al.* 1984), progestogens have been shown to increase incontinence (Caine & Raz 1973) and therefore they may offset any benefit of oestrogen when given as combination therapy to women with genuine stress incontinence.

The findings of this study are similar to those of the double-blind objective study by Walter *et al.* (1978) who did not find any significant effect of oestrogen therapy on either incontinence or the urethral pressure profile. The findings reported by Caine & Raz (1973), Salmon *et al.* (1941), Musiani (1972) and Hilton & Stanton (1983), which all indicated a symptomatic improvement with oestrogens, could be explained by placebo effect. The finding of increased transmission of intra-abdominal pressure to the urethra with oestrogen treatment as reported by Rud (1980) and Hilton & Stanton (1983) could be explained by the higher dosage of oral oestrogen used by Rud (1980) (oestradiol valerate 4 mg daily or oestriol 8 mg daily) or by the intravaginal route of oestrogen administration (Hilton & Stanton 1983) or their microtransducer equipment that is more sensitive than the conventional open-end catheters with constant flow that we used to measure urethral pressures. The clinical significance of this oestrogen-induced increased pressure transmission to the urethra is at present uncertain, as there was no correlation between this and patient's symptomatic improvement (Hilton & Stanton 1983). The risks of high oral dose oestrogen therapy should also be emphasized and it is therefore debatable whether such therapy is justified in genuine stress incontinence.

The significant changes in vaginal cytology and hormone assays with oestrogen treatment confirmed that the patients received the medication. The pre- and post-treatment plasma levels of oestrone and oestradiol were similar to those recorded by J. Hutton (1979 William Blair Bell Memorial Lecture RCOG) after oral administration of 3 mg of piperazine oestrone sulphate. They confirmed that the term hormone 'replacement' therapy is inappropriate since the levels of oestrone and oestradiol were consistently higher than basal premenopausal values.

In conclusion, because of a high placebo response, our study with oral piperazine oestrone sulphate does not confirm the findings of other, mainly uncontrolled, series that oestrogen therapy is effective in reducing genuine stress incontinence.

Acknowledgments

We would like to thank Mrs C. Russell and Mrs M. Reams Assar for their nursing help in this study and Mr Wayne Gillett for his continued encouragement. The work was also supported by Abbott Laboratories.

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Received 3 December 1985
Accepted 13 December 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 575–582

An objective assessment of physiotherapy for female genuine stress incontinence

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Summary. Sixty women with genuine stress incontinence were consecutively assigned to one of four physiotherapy groups who were treated for 6 weeks by either (1) pelvic floor exercises (PFE) in hospital; (2) PFE and faradism; (3) PFE and interferential therapy; (4) PFE at home. Assessment before and after treatment was by 7-day bladder charts, urethral pressure profiles and perineometry. Approximately two-thirds of the hospital-treated patients (groups 1, 2 and 3) experienced marked or moderate subjective improvement and at 6 months, 27% were dry or almost dry. There was little difference in outcome between groups 1, 2 and 3 but hospital-based therapy was more effective than home treatment. Statistical analyses showed that there were significant improvements in the objective indices measured in the 45 hospital-treated patients. Successful treatment was more likely in younger patients, in those with lesser degrees of genuine stress incontinence and those who had had no previous pelvic floor surgery.

It is accepted generally that the most appropriate treatment of severe female genuine stress incontinence is surgical. However, the management of mild to moderate incontinence is less certain and there are some patients for whom surgery is inappropriate—for example, those who are unwilling or not medically fit for surgery and possibly women who wish further pregnancies since later vaginal deliveries may adversely affect successful surgery (Stanton 1979). There is, therefore, a place for conservative treatment of female genuine stress incontinence and physiotherapy is one of the most popular.

There is a significant amount of circularly orientated 'slow twitch' striated muscle within the urethra capable of sustained contraction over long periods, and this may actively contribute to urethral closure and hence continence (Gosling 1979). The activity of the adjacent but separate striated muscle of the pelvic floor also affects continence so that physiotherapy designed to increase the effectiveness of both these striated muscles could be of benefit in genuine stress incontinence.

There has been no detailed objective assessment of the value of physiotherapy in this condition. Kegel (1951) described the use of pelvic floor exercises for incontinence and reported a cure rate of over 80%, and similar results have been recorded by others (Jones & Kegel 1952; Jones 1963). Striated muscle stimulation by faradism (Moore & Schofield 1967) and interferential therapy (McGuire 1975) have been used as an adjunct to pelvic floor exercises but

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there is no agreement on their value (Glen *et al.* 1976). Moreover, none of these studies provided objective assessment of the type and degree of incontinence before and after treatment.

The purpose of this prospective study was to assess objectively the use of pelvic floor exercises alone or with the addition of faradism or interferential therapy in the treatment of women with genuine stress incontinence and to identify the factors contributing to the success or failure of these treatments.

Patients and methods

Sixty patients aged 19–79 (mean 46·8) years were studied. They all had synchronous video pressure-flow cystourethrography (Bates & Corney 1971) and independent flowmetry (Tanmen 1973) investigations and had been diagnosed to have genuine stress incontinence. The diagnosis was made by the absence of involuntary detrusor contraction and the presence, in 25 patients, of an open proximal urethra either at rest or on coughing but without leakage (grade 1), and with leakage (grade 2) in the other 35 women (Whiteside 1973). Twelve patients had had surgery previously to correct incontinence (one woman had grade 1 and 11 had grade 2 incontinence).

Patients were assigned consecutively to one of four therapy groups, 15 women in each group, and they were treated as follows. Group 1 was treated with pelvic floor exercises (PFE) alone; group 2 with PFE plus faradism; group 3 with PFE plus interferential therapy and group 4 with PFE alone at home. Groups 1–3 were treated in the hospital physiotherapy department for 12 sessions over 6 weeks and they were given an instruction sheet describing the PFE to be performed daily at home (Fig. 1). The women in group 4 had one session of PFE in the physiotherapy department and were given an instruction sheet for PFE to be done at home.

Pelvic floor exercises

These exercises, as detailed in Fig. 1, were designed to strengthen the urethral and periurethral striated muscles. A vaginal perineometer, similar to that devised by Kegel (1948), was used during the hospital sessions so that patients were more easily aware of which muscles to contract. It consisted of a compressible silicone rubber air chamber 8 cm long by 3 cm in diameter (with a smaller 1·5 cm diameter model for the older, narrow vagina) connected by plastic tubing to a manometer (Fig. 2). The base of the chamber was expanded so that it rested against the perineum thereby ensuring that distal vaginal squeeze was being measured. As the muscles contracted the manometer registered any increased air pressure within the chamber Patients were instructed to hold each contraction for approximately 5 s then to rest for 15 s. Three series of six contractions were performed with a 2 min rest between each series. The perineometer provided a visual guide of muscle contraction.

Faradism

This involves the use of a low frequency current to stimulate striated muscle contraction. The patient sat with her back supported. A saddle-shaped indifferent electrode (Scott *et al.* 1969) was placed over the sacrum and the active button electrode was applied to the perineum; both electrodes were covered with damp lint. A Minidyn faradic battery provided surges of about 2 s duration at a repetition rate of 12 surges/min, and as strong a current was used as the patient could tolerate comfortably. The patient was instructed to contribute to muscle contraction when the current was felt so that later she could practise the contractions more easily. Three groups of 12 surges were given with a 2 min rest between each group.

Pelvic Floor Exercises

Lie down and relax completely. When you feel relaxed tighten the muscles that stop you passing urine, making sure that all other muscles are relaxed. Hold the contraction for a few seconds then relax completely.

Try to practise this exercise very regularly. At first you will have to lie down or sit to make sure that the muscles are relaxed; later you may be able to practise when standing Do the exercises five times before you get up, five times once you are up, and five times half hourly thereafter. As you feel the contractions getting stronger you may increase them to ten times every half hour

When you are passing water try to stop and start the stream several times. You may find this exercise difficult at first but with practice you will be able to control the stream more easily Again, when you are exercising these muscles, the rest of you must be relaxed completely.

Fig. 1. Patients' instruction sheet for home pelvic floor exercises

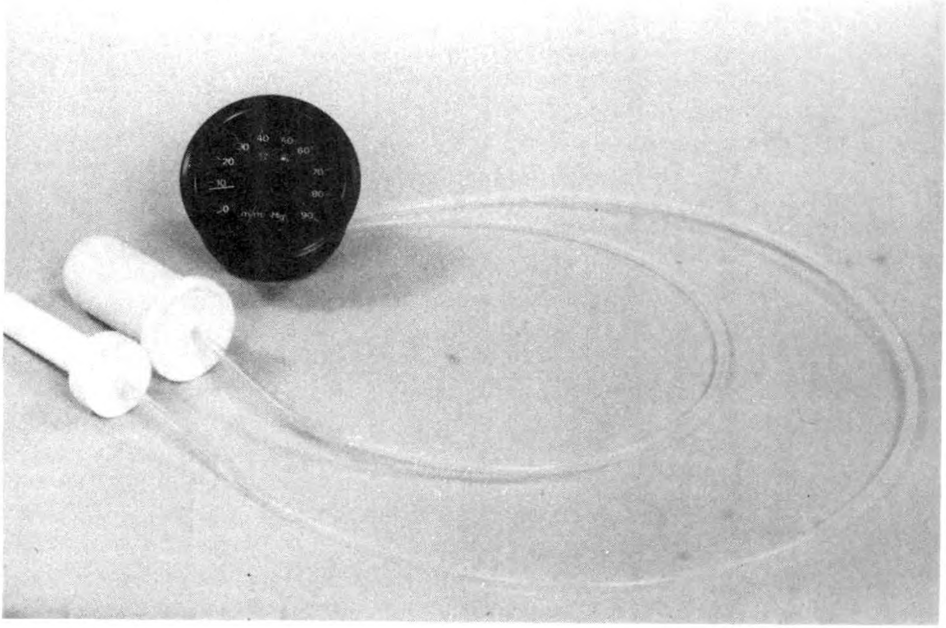

Fig. 2. Perinoemeters

Interferential therapy

This technique produces a low frequency stimulating current within the body while avoiding the problems of skin resistance (Willie 1969). Two different medium-frequency currents of around 4000 cycles/s are applied to the body from different directions. Where the currents cross the intensity of the combined current will increase and decrease rhythmically and the frequency of this 'interference' effect is the difference between the two original frequencies. The regimen described by McGuire (1975) was used. Four medium sized suction electrodes (two each on the abdomen and adductor muscles of the thighs) transmitted a 20–25 mA current which gave 15 pulses at pressure peak 0·25 to 0·30 Pa/cm^2. The first treatment lasted 10 min and the patient remained relaxed during the pelvic muscle stimulation; if no ill-effects were noted the duration of treatment was increased subsequently to 15 min.

Patients in groups 2 and 3 started each hospital session with faradism or interferential therapy, then pelvic floor exercises were performed with the help of the perineometer.

Patient assessment

Subjective assessment was made at 6 weeks and 6 months when patients were asked if they were much improved, improved, or no better than before treatment. Objective assessments were made before and after the 6 weeks of treatment and included the following.

Seven-day bladder chart (Wilson *et al.* 1980). This recorded the frequency of micturition and the number of pad/pant changes per 24 h. Each patient also completed a chart at the 6 month assessment.

Perineometry measurements. These assessed the change in vaginal squeeze after treatment.

Urethral pressure profile. The method described by Brown & Wickham (1969) was used and measurements were taken with the patient at rest and during pelvic muscle contraction. The bladder was filled with 150 ml and the mean value of two consecutive profiles was recorded. Urethral pressure profiles were measured in only 45 patients as this test was only performed after the study had started and also for reasons of poor patient compliance.

Statistical analysis

The four methods of physiotherapy were compared using a standard analysis of variance. An objective assessment of hospital-based physiotherapy was made by comparing the 45 patients in groups 1, 2 and 3 before and after treatment (each patient acted as her own control) using the paired Student's *t*-test. The hospital-treated patients who were considered 'successes' (those who were much improved), and 'failures' (those who were no better) were compared to identifying contributing factors by the two-sample Student's t-test and Fisher's exact test.

Methods, definitions and units conform to the standards proposed by the International Continence Society (Bates *et al.* 1979).

Results

The four treatment groups were comparable with respect to age, weight, parity, severity of leakage and the occurrence of previous surgery for incontinence.

1. Subjective assessment

The results of the 6-week and 6-month assessments are shown in Fig. 3. There was little numerical or statistically significant difference in outcome between the three hospital-based treatments (groups 1, 2 and 3) at the 6 week and 6 month visit. In each group approximately one third considered that they were no better, one third were improved and one third were much improved after treatment; the situation was maintained in most women at 6 months with 16 and 12 of the 44 hospital-treated patients being still 'improved' and 'much improved' respectively. In the home-treatment patients (group 4), only four of the 15 noted any improvement at 6 weeks and 6 months. Although this is numerically fewer than in the hospital-treated groups, the difference was not statistically significant ($P<0{\cdot}10$ at 6 weeks; $P<0{\cdot}30$ at 6 months).

The attendance rates to the physiotherapy department were noted to be better in the faradism and interferential therapy groups than in the group treated by PFE only.

2. Objective assessments

The results are summarized in Table 1.

Frequency of micturition

This was reduced in all the groups. The reductions in the mean numbers of micturitions per 24 h were greater in each of the three hospital-treated groups than in the home-treatment group but the difference was not statistically significant [$F\ (3{,}53) = 0{\cdot}649$, $P = 0{\cdot}587$].

The overall mean reduction in the three hospital-based treatment groups was statistically significant ($P<0{\cdot}0025$).

Pad changes per day

All the treatment groups showed a reduction in the number of pad changes per 24 h and the mean percentage reductions were 54, 43, 52 and 11 in groups, 1, 2, 3 and 4, respectively. The reductions were statistically significant at the 10% level ($0{\cdot}05<P<0{\cdot}1$) in each of the three

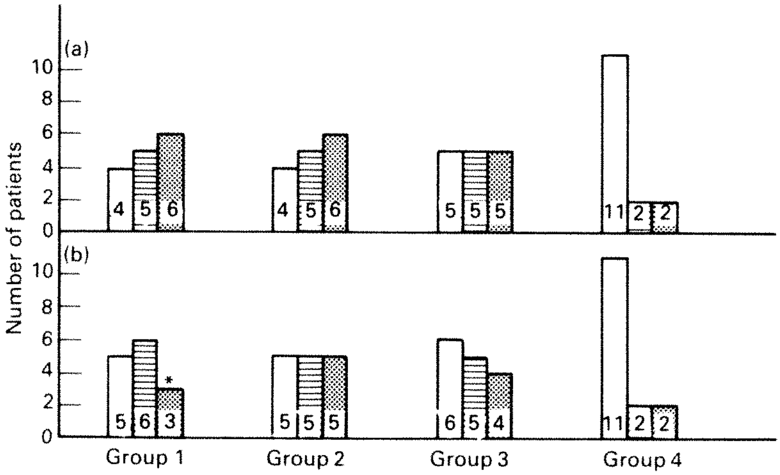

Fig. 3. Subjective comparison of different treatment groups after (a) 6 weeks and (b) 6 months. Group 1, Pelvic floor exercises (PFE) in hospital; group 2, PFE and faradism; group 3, PFE and interferential therapy; group 4, PFE at home. (☐) No better; (▤) improved; (▩) much improved. *One patient did not attend for assessment.

Table 1. Urodynamic variables before and after treatment by different physiotherapy regimens

Variable	Group 1 (PFE in hospital)	Group 2 (PFE + faradism)	Group 3 (PFE + interferential therapy)	Group 4 (PFE at home)	All hospital physiotherapy groups (1, 2 and 3)
Micturitions/24 h					
Before	8·6 (2·7)	8·7 (2·7)	9·1 (3·2)	8·24 (2·7)	8·9 (2·8)
After	7·6 (1·6)	7·8 (2·0)	8·0 (1·8)	8·20 (2·7)	7·9 (1·9)
	($n = 15$)	($n = 15$)	($n = 15$)	($n = 12$)	($n = 45$)
Pad changes/24 h					
Before	2·0 (1·3)	2·3 (2·0)	3·3 (2·7)	3·0 (2·1)	2·5 (2·2)
After	0·9 (1·5)	1·3 (1·4)	1·6 (2·3)	2·7 (2·5)	1·3 (1·8)
	($n = 15$)	($n = 15$)	($n = 15$)	($n = 15$)	($n = 45$)
Perineometry reading (mmHg)					
Before	7·1 (5·4)	5·8 (3·6)	5·1 (4·2)	5·8 (4·4)	6·0 (4·5)
After	15·7 (10·5)	9·0 (5·4)	16·5 (8·3)	6·9 (7·7)	13·8 (8·9)
	($n = 15$)	($n = 15$)	($n = 15$)	($n = 14$)	($n = 45$)
MUCP at rest (cm H_2O)					
Before	49·6 (12·6)	56·1 (14·5)	50·7 (16·1)	49·8 (15·1)	52·6 (16·8)
After	51·5 (10·8)	58·0 (15·4)	56·0 (16·7)	53·4 (16·4)	56·5 (16·5)
	($n = 9$)	($n = 14$)	($n = 12$)	($n = 10$)	($n = 35$)
MUCP + pelvic floor contraction (cm H_2O)					
Before	58·3 (13·4)	62·8 (16·2)	58·1 (17·3)	57·6 (18·7)	60·0 (17·1)
After	62·3 (18·3)	64·4 (14·9)	62·7 (18·4)	62·2 (18·3)	64·3 (16·6)
	($n = 9$)	($n = 14$)	($n = 12$)	($n = 9$)	($n = 35$)

MUCP, Maximum urethral closure pressure.
PFE, Pelvic floor exercise.
Results are means (SD), n is the number of women.

Table 2. Characteristics of 17 'treatment success' and 13 'treatment failures' in a group of 45 patients receiving hospital-based physiotherapy

Variable	Successes		Failures		Statistical significance*
Age (years)	43·8	(10·1)	52	(11·9)	$P<0\cdot05$
Initial no. of pad changes/24 h	1·8	(1·4)	3·9	(2·0)	$P<0\cdot005$
Radiological grade of incontinence	1·4	(0·5)	1·8	(0·4)	$P<0\cdot025$
Initial MUCP (cm H_2O)	59·6	(16·5)	46·6	(15·9)	$P<0\cdot05$
Initial MUCP plus levator contraction (cm H_2O)	70·1	(10·3)	53·3	(17·4)	$P<0\cdot02$
Incidence of previous incontinence-correcting surgery	0		0·46	(0·52)	$P<0\cdot05$*
Parity	2·2	(1·3)	2·5	(1·1)	NS
Weight	63·3	(10·6)	67·3	(5·0)	NS
Micturitions/24 h	9·2	(2·8)	7·9	(3·5)	NS
Initial perineometry reading (mmHg)	6·1	(5·5)	5·1	(3·7)	NS

*The two-sample Student's *t*-test was used for all comparisons except for 'Incidence of previous surgery for incontinence' where Fisher's exact test was used

Results are mean (SD)

hospital-treated group but not in the home-treatment group ($P>0\cdot10$). The reduction in group 3 (PFE + interferential therapy) was significantly greater than that in group 4 (PFE at home) ($P<0\cdot10$) but there were no other significant differences between the groups.

The overall reduction in the three hospital-based treatment groups at 6 weeks was statistically significant ($P<0\cdot0005$); at 6 months after treatment the mean number of pad changes per 24 h was 1·5, and this was still significantly lower than the mean number (2·5) before treatment ($P<0\cdot005$).

Perineometry

The perineometry readings were increased in all groups and the mean percentage increases ranged from 224% in group 3 (PFE + interferential therapy) to 19% in the home-treatment group. The increases were statistically significant at the 5% level ($P<0\cdot05$) in groups 3 and 1 (PFE in hospital), and at the 10% level ($0\cdot05<P<0\cdot10$) in group 2 (PFE + faradism). The increase in the home-treatment group was not statistically significant ($P>0\cdot10$). The changes in groups 3 and 1 were significantly greater than those in the home-treatment group ($P<0\cdot05$) There were no other significant differences between the groups.

Analysis of the 45 hospital-based patients as a group showed a significant increase in perineometry readings from 6·0 mmHg before to 13·8 mmHg after treatment ($P<0\cdot0005$).

Urethral pressure profiles

Results were available for only 45 patients.

Maximum urethral closure pressure (MUCP) at rest. The mean MUCP was increased in all groups, but the increase was statistically significant only in group 3 (PFE + interferential therapy) ($P<0\cdot05$). There were no other significant differences between the groups. Overall the three hospital-based groups the mean increase was significant from 52·6 to 56·5 cm H_2O ($P<0\cdot005$).

MUCP during pelvic floor muscle contraction. The mean value was also increased in each of the four groups, but there were no statistically significant differences in the increases between the four groups [$F\,(3,40) = 0\cdot725$, $P = 0\cdot543$]. The mean increase in the hospital-based patients overall was significant ($P<0\cdot01$).

Regarding the 10 women undergoing hospital-based physiotherapy who did not have urethral pressure profilometry, their subjective assessment was similar to the main group with three patients being no better, four improved and three much improved.

Factors contributing to success or failure in hospital-based treated patients

A comparison of the 17 patients considered to be 'successes' (i.e. much improved) with the 13 'failures' (i.e. no better) of the 45 hospital-treated patients is presented in Table 2. The most significant factor associated with successful treatment was the initial number of pad changes per 24 h; this was 1·8 in the successes compared with 3·9 in the failures ($P<0{\cdot}005$). The successful patients were also significantly younger (43·8 compared with 52 years, $P<0{\cdot}05$) and they had less evidence of urethral incompetence on radiological screening (mean grade of incontinence was 1·4 in successes compared with 1·8 in failures, $P<0{\cdot}025$). The initial MUCP both at rest and during pelvic floor contraction was significantly higher in the successes than in the failures. None of the successful patients had had previous surgery for incontinence compared with six of the 13 failures (five had had previous pelvic floor surgery and one had had a retropubic procedure). This difference in the occurrence of previous surgery was also statistically significant ($P<0{\cdot}05$). The non-significant factors associated with successful treatment included parity, weight, micturitions per 24 h and initial perineometer reading.

Discussion

The results of the subjective and objective assessments confirm the benefits of intensive hospital-based physiotherapy compared to a single physiotherapy session plus an instruction sheet for home use in women with genuine stress incontinence. The patients studied were from a urodynamic referral centre and approximately 20% had undergone previous incontinence surgery. However, two thirds of them were improved by hospital-based physiotherapy and this effect was sustained in the majority at 6 months with 27% of patients being dry or almost dry at this time. A longer term study would assess the duration of effect but it is probable that prolonged benefit depends on continuation of the exercises by the patient.

The addition of interferential therapy or faradism does not appear to confer any significant benefit over pelvic floor exercises alone but the three groups of hospital-based patients showed significant improvement compared with the home-treatment group. The patients who received additional electrical therapy had a better attendance record and this finding was also noted by Scott & Hsueh (1979); they attributed it to better patient motivation with the more impressive equipment.

Concerning the objective measures investigated in the women receiving hospital-based physiotherapy, there was a significant reduction in leakage, as recorded by pad changes and the number of micturitions per 24 h. The mechanism of this reduction in the frequency of micturition is unknown but it may add support to the theory that pelvic floor contraction can inhibit the detrusor motor nucleus (Bradley *et al.* 1974). More simply, this reduction could be explained by less fear of leakage following treatment, as patients often compensate for incontinence by frequent voiding in order to keep their bladder empty.

The significant increases in maximum urethral closure pressure and perineometer readings may suggest that both the urethral and periurethral striated muscles are affected by physiotherapy. However, further studies are required to substantiate this. The mean increase of 4 cm H_2O in the urethral pressure profile after treatment should be interpreted with caution as the instrumental variability between consecutive measurements has been estimated to be 4 cm H_2O (Abrams *et al.* 1978).

The results confirm the findings of Kegel (1948) and Mandlestam (1976) that the perineometer is a useful device for teaching the patient pelvic muscle contraction. Also it allows an objective assessment of contractility and encourages patients during treatment. All hospital treatment was supervised by two physiotherapists and the success of treatment is probably as dependent on their enthusiasm as on patient motivation.

The severity of incontinence was shown to be a significant prognostic indicator as mild-moderate incontinence was improved more consistently than severe leakage. Jones & Kegel (1952) did not observe this phenomenon nor did they find that failure was more commonly associated with previous incontinence surgery and older age as indicated here. In this study the successful factors of younger age and less pelvic floor surgery may be due to better tone and less fibrosis of the pelvic musculature although other factors may be involved.

Acknowledgments

We are indebted to Mr Brian Faragher, Senior Medical Statistician, University Hospital South Manchester, United Kingdom, for his help in the statistical analyses in this paper. We are grateful also to Mrs Margaret Reams Assar and Mrs Charmian Russell for their nursing assistance in this study and to Mr Wayne Gillett for his advice and encouragement.

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Received 3 December 1985
Accepted 24 November 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 583–588

Combination chemotherapy followed by surgery or radiotherapy in patients with locally advanced cervical cancer

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Summary. Forty-seven patients with locally advanced cervical cancer at high risk of relapse received three cycles of chemotherapy with PVB (cisplatin, vinblastine and bleomycin) before definitive local treatment with either radical surgery or radiotherapy. Thirty-one of the 47 patients (66%) responded to initial chemotherapy, and 11 of them have relapsed compared with 13 of the 16 non-responders. Median time to recurrence was 31 weeks for PVB non-responders but has not yet been reached for PVB responders. After a median follow-up of 128 weeks, 14 of the 31 responders (45%) are alive and disease free compared with 3 of the 16 non-responders (19%). There was a positive correlation between response to chemotherapy and subsequent response to radiotherapy. PVB was in general well tolerated although one death is probably attributable to chemotherapy. A randomized study comparing radiotherapy alone with initial PVB chemotherapy followed by radiotherapy is in progress.

Early stage cervical cancer is curable by surgery or radiotherapy, but cure rates fall sharply with more advanced stage disease (Hanks *et al.* 1983; Perez *et al.* 1983; Jampous *et al.* 1975). Radiotherapy is the mainstay of treatment of locally advanced cervical cancer with the clinical stage and tumour bulk being the major predictors of pelvic recurrence after radiotherapy (Piver & Chung 1975; Mendenhall *et al.* 1984). Both also correlate with frequency of lymph node metastases (Piver & Chung 1975). The incidence of distant failure after radiotherapy is predicted by the initial clinical stage (Perez *et al.* 1983; Jampous *et al.* 1975). Strategies to improve the results of primary treatment in patients with locally advanced cervical cancer are directed toward improved local control as well as effective management of lymph node and presumed microscopic distant metastases.

Several approaches including the use of

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Table 1. Chemotherapy regimen for carcinoma of the cervix

Day 1	Vinblastine	4 mg/m^2 i v.
	Bleomycin	15 mg (total dose) i.m.
	Cisplatin	60 mg/m^2 i.v. with standard hydration and mannitol diuresis*
Day 2	Vinblastine	4 mg/m^2 i.v.
Days 8 and 15	Bleomycin	15 mg i.m.

* Standard hydration=1 litre 2·5% dextrose saline over 1 h and 100 ml 20% mannitol over 15 min before infusion of cisplatin in 1 litre normal saline over 1–2 h depending on cisplatin concentration Post hydration comprises 2 litres of 2·5% dextrose saline over 8 h.

hypoxic cell sensitizers and hyperbaric oxygen have been adopted to enhance local control by radiotherapy. In addition, radiotherapy fields have been extended to include the para-aortic nodes in patients with a high probability of para-aortic nodal metastases but the morbidity of this approach is significant. None of these approaches is likely, however, to prevent the development of distant metastases in those patients in whom microscopic metastases are already present at the time of primary treatment.

The role of chemotherapy in the management of patients with carcinoma of the cervix has not yet been defined. A number of cytotoxic drugs induce regressions in cervical cancer but cisplatin based programmes appear to have the highest tumour response rates (Friedlander *et al.* 1983; Rosenthal *et al.* 1983; Bloch *et al.* 1984; Alberts *et al.* 1981). We have used combination chemotherapy comprising cisplatin, vinblastine and bleomycin (PVB) in the management of patients with metastatic and recurrent carcinoma of the cervix and reported an overall tumour response rate of 69% (Friedlander *et al.* 1983). We have subsequently used the same regimen to reduce tumour bulk before definitive local treatment in patients with locally advanced cervical cancer with a high risk of relapse (Friedlander *et al.* 1984). The initial report described the tumour response rate in 30 patients but at that time follow-up was short. We now describe our experience using PVB before radical surgery or radiotherapy in the management of 47 patients presenting with locally advanced carcinoma of the cervix. Median follow-up in the series is now 128 weeks (range 66–258 weeks).

Patients and methods

Forty-seven patients with histologically confirmed carcinoma of the cervix, initially unsuitable for radical surgery, were studied. Most patients had between Stage IIb and IVa disease but patients with Stage Ib and IIa disease with large non-resectable lymph node metastases, discovered at exploratory laparotomy, or large primary tumours were also included in the series. All patients had measurable disease and an ECOG performance status of 0–3. Patients gave informed consent to the treatment programme which was explained as comprising three courses of combination chemotherapy followed by local treatment—either surgery or radiotherapy depending on the tumour response.

Pretreatment investigations routinely performed included a complete blood count, serum biochemical screen, serum carcino-embryonic antigen (CEA) estimation, chest roentgenogram, excretory urography, cystoscopy and abdomino-pelvic ultrasound. Radionuclide liver scans and abdomino-pelvic computed tomography scans were performed where appropriate. A full audiogram and single breath diffusing capacity for carbon monoxide were performed before the first and third chemotherapy cycles Patients with impaired renal function or deranged liver function tests were not included in the series. None of the patients had received chemotherapy or radiotherapy previously.

The chemotherapy regimen is detailed in Table 1. Patients were admitted to hospital overnight to receive cisplatin treatment but received the weekly bleomycin as out-patients. In patients without disease progression three courses of PVB were administered before a decision was made on subsequent local management. In patients with disease progression chemotherapy was stopped and radiotherapy commenced immediately.

Response to chemotherapy was assessed according to the criteria established by Miller *et al.* (1981) by clinical measurement and ultrasound. After three courses of chemotherapy, the majority of patients were treated with pelvic radiotherapy but in some patients with a dramatic reduction in tumour size, a radical hysterectomy and pelvic lymphadenectomy was performed and radiotherapy administered subsequently to those with lymph node metastases.

Pelvic radiotherapy was usually started in the second week of the final cycle of PVB chemotherapy. Patients received 50 Gy in 25 daily fractions over 5 weeks as external beam radiotherapy followed by intracavity radium where anatomically feasible. Survival and time to disease progression or relapse were calculated from the date of initial diagnosis. Survival, calculated from the date of completion of chemotherapy, was also compared in responders and non-responders to chemotherapy and in accordance with the landmark method proposed by Anderson *et al.* (1983) for analysis of survival by tumour response category. Median follow-up was calculated from the date of commencement of chemotherapy to time of analysis for each patient. The sites of recurrence were also documented.

Results

Patient characteristics

Table 2 details the clinical stage of the 47 patients. There were eight patients with bulky Stage Ib tumours, four of whom were found at initial exploratory laparotomy to have large fixed nodal metastases. The other four patients had large primary tumours with a mean tumour diameter of 6 cm. Of the eight patients with Stage IIa tumours, one was unfit for operation on medical grounds, while the remainder had large primary tumours.

Response to chemotherapy

Table 2 illustrates the clinical response to chemotherapy in the 47 patients studied. In 31 (66%) patients there was partial or complete response and only three had obvious disease progression during chemotherapy. The majority of tumour responses were clearly evident on clinical examination at the time of commencing the third course of chemotherapy (6 weeks after starting treatment). Factors possibly predicting response to chemotherapy were assessed by stepwise logistic regression. Factors considered were disease stage and histological features of the primary tumour, i.e. nuclear grade, number of mitoses, degree of lymphoplasmocytic infiltration and histological type. Histology was reported by two gynaecological pathologists. Only moderate to intense lymphoplasmocytic infiltration of the primary tumour was significantly correlated with subsequent response to chemotherapy, with 89% of these patients responding compared with 55% of patients with mild inflammatory response. There was one patient each with adenocarcinoma or small cell carcinoma variants, and it is not possible to say whether the response of these cell types is similar to that of squamous tumours.

Table 2. Clinical stage and response to chemotherapy

		Response			
Stage	No.	CR	PR	NC	PD
Ib	8	—	5	3	—
IIa	8	—	7	—	1
IIb	13	1	5	6	1
IIIa	7	3	3	1	—
IIIb	10	1	5	3	1
IV	1	—	1	—	—
	47	5	26	13	3

CR, Complete response; PR, partial response; NC, no change; PD, progressive disease.

Subsequent treatment

Table 3 documents the subsequent treatment following completion of chemotherapy.

Radical surgery. Radical hysterectomy and pelvic lymphadenectomy was performed in 15 patients, comprising five clinical complete responders, nine partial responders and one patient who, while not achieving partial remission, nevertheless had had sufficient regression of a large Stage IB tumour to permit radical surgery. Operative specimens of the primary tumour in all showed residual microscopic disease and there was residual macroscopic disease in the partial responders. Four of the 14 patients responding to PVB had invasive lymph node metastases at subsequent radical surgery. They received adjuvant pelvic radiotherapy postoperatively. One other responder had a tumour lymphatic embolus in a solitary lymph node without parenchymal invasion: she was not treated further. In the patient achieving less than

Table 3. Response to chemotherapy, subsequent local treatment and outcome in 47 patients

		Subsequent treatment				Recurrence		
Response to chemotherapy	Total	RHPL	RHPL+ ADJ R/T	R/T	R/T+ ADJ SURG	Nil	Local	Distant
Complete	5	3	—	—	—	—	1	—
		—	2	—	—	—	1	—
Partial	26	7	—	—	—	—	1	1
		—	2	—	—	—	2	—
		—	—	13	—	—	2	—
		—	—	—	1	—	—	—
		—	—	—	—	3	1	—
No change	13	0	—	—	—	—		
		—	1	—	—	—	—	—
		—	—	11	—	—	8	—
		—	—	—	1	—	1	—
Progressive disease	3	—	—	3	—	—	3	—
	47	10	5	27	2	3	20	1

RHPL, Radical hysterectomy and pelvic lymphadenectomy, RHPL+ADJ R/T, RPHL+adjuvant radiotherapy; R/T+ADJ SURG, radiotherapy+adjuvant surgery

partial remission to chemotherapy, the operative specimen revealed persisting central disease and lymph node metastases. She subsequently received adjuvant pelvic radiotherapy.

Radiotherapy. Twenty-nine patients, 14 of whom had responded to PVB, had radiotherapy as the definitive local treatment. Response to radiotherapy was seen in all chemotherapy responders but in only 7 of 15 PVB non-responders. One patient thought unlikely to return for follow-up for geographic reasons had radical hysterectomy after radiotherapy.

No further treatment. Three partial responders to PVB had no further treatment two of them refused treatment; one returned to her home overseas where she died of progressive cancer and the other opted for alternative non-medical treatment and has been lost to follow-up. The third patient died suddenly outside hospital one week after completing chemotherapy and before commencing radiotherapy. The cause of death was not established.

Recurrence

The pattern of recurrence is shown in Table 3 and the time to disease recurrence after chemotherapy and local treatment in Table 4. Overall

Table 4. Median survival and tumour recurrence by clinical stage and response to initial chemotherapy

			Patients with relapse			Median time to relapse (weeks)	
Stage	Total no. of patients	Median survival (weeks)	Total no.	PVB responders	PVB non-responders	PVB responders	PVB non-responders
Ib	8	54	5	2/5	3/3	NYR	30
IIa	8	NYR	3	2/7	1/1	NYR	36
IIb	13	NYR	7	2/6	5/7	NYR	50
IIIa	7	57	5	4/6	1/1	NYR	23
IIIb	10	86	4	1/6	3/4	NYR	31
IVa	1	12	0	0/1	—	—	—

PVB, Cisplatin, vinblastine and bleomycin chemotherapy; NYR, not yet reached.

24 of 47 patients (51%) have relapsed. There was a marked difference in relapse rates between chemotherapy responders and non-responders Thirteen of 16 non-responders to chemotherapy have relapsed (81%), 12 with local recurrence and one with both local and distant metastases. The other three non-responders to chemotherapy currently remain disease free. By contrast 11 of the 31 chemotherapy responders (35%) have relapsed (P=0·003, Fisher's exact test).

Recurrence was also analysed according to the type of local treatment used after chemotherapy. Among the 14 responders who had surgery as their definitive mode of treatment, seven including all five shown to have nodal metastases following PVB, have relapsed.

All but one of the 29 patients having irradiation as their definitive local treatment received at least 50 Gy as external beam radiotherapy Additional intracavity radium was administered to 8 of the 14 chemotherapy responders and 10 of the 15 non-responders. Twelve of the 15 PVB non-responders (80%) but only 3 of the 14 responders (21%) have relapsed following radiotherapy. Median time to failure after radiotherapy has not yet been reached for chemotherapy responders and is 36 weeks for chemotherapy non-responders (P<0·001). Table 4 describes relapse and time to treatment failure according to clinical stage at presentation and response to chemotherapy.

Survival

At the time of this analysis, 26 of the 47 patients have died. Median survival for all patients is 88 weeks. Survival by disease stage is shown in Table 4. Twelve of the 16 patients not responding to chemotherapy (75%) have died of progressive disease. Among responders, 14 (45%) have died, 8 (26%) of progressive disease and 6 of other causes (3 ischaemic heart disease and 1 each of thyrotoxic heart disease, breast cancer and unknown cause). Median post-chemotherapy survival was 45 weeks for non-responders and 117 weeks for responders (P=0·03, Mantel–Cox).

Toxicity

Details of toxicity of this chemotherapy programme were similar to those reported previously (Friedlander *et al.* 1984). There were no unexpected problems with pelvic irradiation in patients who had received prior chemotherapy nor was radical hysterectomy more complicated than in previous untreated patients.

Discussion

This report updates our earlier experience using PVB chemotherapy prior to local treatment among patients presenting with locally advanced disease. Previous studies have shown that bulky local disease is a frequent cause of failure to control local tumour by pelvic irradiation (Piver & Chung 1975; Mendenhall *et al.* 1984). It was hoped that reduction in tumour bulk before radiotherapy might improve local control rates, and our results suggest that this may have been accomplished. Our data also suggest that responders to chemotherapy have an improved rate of local control by radiotherapy and prolonged survival compared with non-responders. While this may reflect a beneficial effect of chemotherapy, response may merely be a marker for an intrinsically better prognostic group. This point will require further study.

The finding that tumours which respond to chemotherapy are also much more likely to respond to radiotherapy is of particular interest. While reduction in tumour mass might be expected to improve local control rates (Baker *et al.* 1981), local control by radiotherapy is infrequent amongst patients whose tumour did not regress on chemotherapy and this suggests that there may be some relation between failure to respond to chemotherapy and radio-resistance

It is also of interest that patients with bulky Stage Ib tumours in our series, irrespective of their response to chemotherapy, appear to have a worse prognosis than patients with more advanced pelvic disease. These findings suggest that the biology of bulky Stage Ib, IIa disease may be more aggressive than that of more extensive locally advanced disease. Piver & Chung (1975) have reported that 5-year survival figures for Stages Ib and IIa disease fall markedly with increasing size of the cervical tumour. Where the diameter of the primary lesion was 6 cm or greater, only 3 of their 6 patients with Stage Ib disease and 5 of 13 with Stage IIa disease survived 5 years. They also noted that increasing numbers of pelvic nodal metastases were associated with a worsening prognosis, with only about 15% 5-year survival being achieved for their patients with Stage Ib, IIa disease when there were four or five pelvic lymph nodes containing metastases (Piver & Chung 1975). Our patients with poor prognosis Stage Ib, IIa disease appear to confirm these reports.

We conclude that initial chemotherapy with cisplatin, vinblastine and bleomycin is effective in reducing tumour bulk before definitive local treatment in patients presenting with locally advanced carcinoma of the cervix. Based upon our experience, a randomized controlled trial has been launched comparing a policy of initial PVB chemotherapy followed by radiotherapy with standard therapy using radiotherapy alone.

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Received 20 June 1986
Accepted 24 October 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 589–591

Metastatic germ cell tumour associated with XY gonadal dysgenesis: successful chemotherapy. Case report

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Case report

A 20-year-old nulligravid, single, phenotypic female was investigated in 1976 at the Belfast City Hospital for primary amenorrhoea and hirsutism. She was a healthy woman with normal distribution of body hair, hirsute upper lip and arms, early breast development only, an enlarged clitoris, marked muscular development of her shoulders and moderate mental handicap (IQ 61). The main initial abnormal biochemical finding was of a raised testosterone of 166 mg/100 ml (normal range 40–110 mg/100 ml). Laparotomy revealed that the right ovary was replaced by a streak but her uterus and tubes were normal. A left salpingo-oophorectomy was performed. The histology showed a mixed ovarian tumour with elements of gonadoblastoma, dysgerminoma and haemorrhagic areas suggestive of choriocarcinoma. The plasma testosterone, which was elevated, fell to normal. Postoperatively her abnormal endocrine investigations were: plasma FSH 74 u/l (normal range 0·6–7·5 u/l) and plasma LH 100 u/l (normal range 0·8–16 u/l).

In 1977 she developed left-sided pleuritic chest pain and haemoptysis. Screening for tuberculosis was negative. In the chest she was dull at the left base with signs compatible with pleural effusion. Pelvic examination was normal. Pleural biopsy revealed malignant cells infiltrating the pleura. Serum human chorionic gonadotrophin (hCG) and alpha-fetoprotein (AFP) concentrations were 18 510 i.u./litre and 3 kU/litre, respectively; the pleural fluid hCG and AFP concentrations were 37 258 i.u./litre and 13 kU/litre, respectively. The serum:CSF hCG ratio was 93:1 and her brain scan was normal. In the absence of a pregnancy, the grossly elevated hCG concentration was highly suggestive of a metastatic germ cell tumour containing a major trophoblastic element. Chromosomal analysis showed a 46 XY karyotype.

As soon as her chest infection was controlled with antibiotics she was started on cytotoxic chemotherapy with POMB/ACE (Newlands *et al.* 1983). The initial treatment was with two courses of POMB (cisplatin, vincristine (Oncovine), methotrexate and bleomycin) which was followed by ACE (actinomycin D, cyclophosphamide and etoposide). She had central nervous system prophylaxis with four injections of intrathecal methotrexate (12·5 mg). She received a total of nine courses of chemotherapy which she tolerated satisfactorily and the serum hCG fell to the normal range by the fifth week (Fig. 1). By November 1977 a residual mass persisted at the left base in the chest. This was excised and histology showed only necrotic tissue.

Since 1977 she has been on regular clinical and biochemical follow-up and serial hCG and AFP concentrations have all remained normal to the end of 1985. At this stage it is unlikely that she will have further recurrence from her germ cell tumour.

Comment

The association between gonadal dysgenesis and germ cell tumours is long established (Scully

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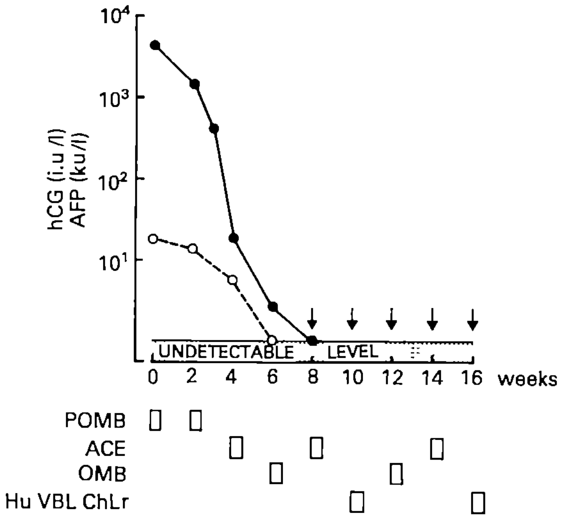

Fig. 1. Response of the tumour markers hCG (human chorionic gonadotrophin) and AFP (alpha-fetoprotein) to combination chemotherapy in a 21-year-old woman with metastatic germ cell tumour arising from XY dysgenetic gonad POMB, cisplatin, vincristine (Oncovin), methotrexate, bleomycin; ACE, actinomycin D, cyclophosphamide, etoposide, Hu VBL Chlr, hydroxyurea, vinblastine, chlormabucil

1970). Most patients are chromatin negative and have a Y chromosomal component (Teter & Boczkowski 1967) but a small proportion have been found to have XO and XX karyotypes (Schellhas *et al.* 1971). Gonadoblastoma is the most commonly associated tumour (Schellhas 1974) and some produce androgens (Scully 1970) which were found in our patient.

Although there are no literature reports of metastatic gonadoblastoma, its importance lies in the association with dysgerminoma in about 50% of cases (Gallager & Lewis 1973) as well as the occasional presence of elements of embryonal carcinoma, yolk sac as well as choriocarcinoma. It is also estimated that the risk of malignancy in dysgenetic gonads of patients with a Y chromosome content is approximately 25% (Schellhas 1974).

The development of metastatic chest lesions in this patient seemed to contradict earlier suggestions that conservative surgery could be adequate in patients with gonadoblastomas arising in dysgenetic gonads regardless of the patient's age and histology (Teter 1970). It is therefore a safer policy, as suggested by Talerman (1971), to excise the other ovary which may contain microscopic tumour.

While the prognosis in gonadal dysgenesis with localized tumours is good (Scully 1970; Teter 1970; Talerman 1971; Hart & Burkons 1979), little is known about the survival data of patients with metastatic germ cell tumours. Talerman (1974) gave a generally gloomy picture of patients with gonadoblastoma and embryonal carcinoma, yolk sac or choriocarcinoma elements. None of the patients he reviewed survived for longer than 18 months. Three of the four patients with metastatic dysgerminoma reviewed by Schellhas *et al.* (1971) had radiotherapy. The patient reported by Hart & Burkons (1979) had chemotherapy and died 3 months later.

There are no previous reports of successful chemotherapy in any patient with metastatic germ cell tumour arising in a dysgenetic gonad. This thus constitutes the first report of successful chemotherapy as well as disease-free survival of >8 years.

Our findings highlight the need for extensive histological sampling of the specimen, optimum surgery comprising at least bilateral adnexectomy and prolonged follow-up with regular assays for the tumour markers hCG and AFP. It would appear that malignant germ cell tumours arising from XY dysgenetic gonads, as in our patient, exhibit the same biological behaviour and chemotherapeutic responsiveness as in patients with normal gonads (Newlands *et al.* 1982; Newlands & Bagshawe 1986). Even if malignant germ cell tumour components are absent, patients should be followed up for life since metastatic lesions can develop up to 9 years later, as evidenced by the report of Gallager & Lewis (1973).

The main developments in chemotherapy for germ cell tumours of the ovary have been recently reviewed. Slayton *et al.* (1985) discussed the results in 76 patients treated with VAC chemotherapy, and Williams *et al.* (1984) have summarized the results and limitations of using PVB chemotherapy. Newlands & Bagshawe (1986) discussed the relative merits of the various chemotherapeutic regimens in more detail. Using POMB/ACE chemotherapy, the survival in patients who had not received prior radiotherapy or chemotherapy is currently 88%.

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Received 2 June 1986
Accepted 6 August 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 592–593

Left atrial myxoma in the second trimester of pregnancy. Case report

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Case report

The 31-year-old patient booked in at the City Hospital, Nottingham, in her third pregnancy at 15 weeks gestation with symptoms of increasing dyspnoea on exertion, night sweats and palpitations. She reported few problems with her first pregnancy that had ended successfully 7 years previously, but she had been short of breath and had a 'chest infection' during the 12 weeks of her second pregnancy, which ended in spontaneous abortion the previous year. She had continued to be dyspnoeic since but had not consulted anyone about her symptoms which had become progressively worse during this pregnancy. On examination she was noted to have a loud diastolic murmur. Digoxin, 0·25 mg daily, was started and she was referred for a cardiological opinion and echocardiogram. There was some deterioration in the next week and the digoxin dose was increased. An echocardiograph at 18 weeks gestation showed typical features of a left atrial myxoma.

She was immediately transferred to Groby Road Hospital cardiothoracic unit where a large left atrial myxoma, histologically confirmed, was excised under cardiopulmonary bypass. Premedication was with diazepam and droperidol. Peri-operative analgesia was obtained with one dose of levorphanol at induction. She was ventilated to a $P\text{CO}_2$ of 5 kPa and there were no episodes of hypoxia, as monitored by serial blood gases. No volatile agents or vasoconstrictors were required. The 2-h operation was uneventful except for A-V dissociation immediately after bypass which required temporary cardiac pacing. She was extubated 10 h post-induction and required minimal inotropic (dopamine) support for 20 h. The fetal heart was monitored intermittently by Doppler for the next week. Although fetal movements were decreased for 3 days, the fetal heart rate remained within normal limits.

The patient made a good recovery and the pregnancy progressed normally with fetal growth monitoring by serial ultrasound scans.

As the pregnancy approached term, she experienced increasing pain at the site of the sternal split. Labour was induced at 39 weeks gestation and she was delivered of a 3·3 kg, live female infant by forceps under epidural analgesia because of sternal pain with pushing. Mother and infant had a normal postnatal course.

The patient will be followed up for recurrence of the tumour by echocardiography.

Discussion

Although atrial myxomas are rare with an incidence of 8 per million autopsies (Donahoo *et al.* 1979), they are the commonest primary cardiac tumour and are readily amenable to surgical removal, with excellent postoperative prognosis. Prompt diagnosis and intervention are important, as potentially fatal obstructive and embolic complications may occur. Only four case reports of atrial myxoma during pregnancy have been published. Sejhar & Vambera (1982) reported a 29-year-old woman whose pregnancy was aborted in the third month before surgical removal of the left atrial myxoma. Two other patients were a 39-year-old woman (Casarotto *et al.* 1979) and a 26-year-old woman (Trimakas *et al.* 1978) who underwent excision of the tumour

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under cardiopulmonary bypass without interrupting their pregnancies at 21 and 23 weeks gestation, respectively. Both patients gave birth to live, normal infants at term. The fourth patient was a 28-year-old women in whom a left atrial myxoma was diagnosed at 30 weeks gestation (Elston 1984). She was managed medically for 5 weeks when she developed congestive cardiac failure and was delivered by caesarean section under epidural anaesthesia. A week after delivery she decompensated further and the left atrial myxoma was removed.

The diagnosis of organic obstruction of the left side of the heart is more difficult during pregnancy since up to 60% of pregnant women complain of dyspnoea, often associated with exercise, and worse in recumbency, and many normal pregnant women also have a systolic murmur at the base of the heart. Early diagnosis and treatment are important since the circulating blood volume increases to 50% above normal during pregnancy which may precipitate subsequent deterioration in the patient with mitral valve obstruction, as was seen in our patient. The complications of embolization depend on the site embolized and may be minimal or fatal. Cardiac catheterization was recommended for all patients suspected of having obstruction of the mitral valve but this technique is not advised in the pregnant patient (Gardin 1982). With advances in echocardiography this non-invasive technique which easily distinguishes left atrial myxoma from the more common mitral stenosis has rendered diagnostic cardiac catheterization obsolete.

Although recurrence of the tumour is rare, in young patients long-term follow-up with echocardiography is indicated.

Acknowledgments

We wish to thank Mr J. N. Leverment, consultant cardiothoracic surgeon, and Dr David Banks, consultant physician, for their permission to report this interesting case.

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Received 27 January 1986
Accepted 19 February 1987

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 594–595

Cord prolapse—can we save more babies? Case reports

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Case reports

Patient 1

A 39-year-old booked patient, parity 5 + 0, was admitted in early labour. She was at term and had ruptured her membranes 1 h before admission. On examination, a non-pulsatile prolapsed cord was found at the introitus and the cervix was 5 cm dilated. Auscultation with a Pinard stethoscope and Doppler technique failed to detect fetal heart sounds. The baby was diagnosed as dead and a vaginal delivery was planned. On ultrasound examination by real-time scanning, however, the fetal heart was beating at about 80 beats/min and in less than 15 min, a live male infant was born by caesarean section under general anaesthesia. He weighed 3045 g with Apgar scores of 8 and 10 at 1 and 5 min respectively. Mother and baby were well when discharged 7 days later.

Patient 2

A 28-year-old unbooked patient, parity 1 + 0, was admitted at 29 weeks gestation from a peripheral clinic because of a prolapsed arm and prolapsed cord which were said to have occurred 4 h before arrival. She was in labour and on examination the cervix was 3 cm dilated with a non-pulsatile cord palpable by the prolapsed arm. The fetal heart was not detected with a Pinard stethoscope or Doppler technique and an intrauterine death was diagnosed Ultrasound examination was performed immediately to determine fetal size and the heart was seen beating at about 50 beats/min. Caesarean section was performed under general anaesthesia and within 20 min, a live 1270 g male infant was born with Apgar scores of 2 and 3 at 1 and 5 min respectively. He died after 3 h of respiratory failure. There was also clinical evidence of congenital syphilis.

Discussion

The management of prolapsed cord in a viable fetus is generally agreed upon (Goldthorp 1967; Kettle 1967; Savage *et al.* 1970). More recent advances in its management hold promise for improvement in fetal salvage (Katz *et al.* 1972; Levy *et al.* 1984). Our finding of the presence of fetal heart movements by ultrasound in the absence of cord pulsation and audible fetal heart sounds should further reduce the perinatal mortality rate.

Fenton & D'Esopo (1951) reported 36 singleton pregnancies complicated by a prolapsed non-pulsatile cord in the absence of fetal heart sounds. Vaginal delivery was allowed and unexpectedly three (8·4%) of the patients were delivered of living babies. Despite this, however, it is generally accepted that a non-pulsatile prolapsed cord with absence of fetal heart sounds is diagnostic of fetal death. This premise is challenged in the light of our experience and may be no longer legally defensible if ultrasound facilities are available.

The prospect of brain damage in a baby whose heart is too feeble to be heard by Doppler is a valid anxiety. It is felt, however, that in severe anoxia, extreme bradycardia or even the absence of the fetal heart beat does not preclude successful resuscitation. Fetal systemic response to asphyxia such as severe bradycardia may occur without producing subsequent encephalopathy (Fenichel 1983; Scott 1976; Thomson *et al.* 1977).

A real-time ultrasound machine is now becoming standard equipment in most labour

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wards. Even junior medical staff are expected to have a basic knowledge of its use. There should be immediate recourse to it in all cases of prolapsed cord, unless pulsation is obvious and the fetal heart sounds are easily heard. This approach should simplify management and improve fetal salvage. Repeated palpation of the cord, when pulsation is in doubt, may cause spasm of the vessels and prejudice the fetal outcome. Auscultation can be unsatisfactory and subjective given the emergency state that prevails when a cord is prolapsed, especially if a fetal bradycardia approaches the maternal heart rate. In our cases, the clinical diagnosis proved inaccurate even with the involvement of senior staff.

Allowing vaginal delivery in cases of presumed fetal death would seem to carry the risk of losing a number of salvagable babies. We feel that to determine fetal status in the absence of cord pulsation, emphasis should not be on hearing the fetal heartbeats, but on seeing them. Seeing is believing.

Acknowledgments

We wish to thank Dr K. D. Bolton FCP (SA), Head of the Department of Neonatatology for his contribution to this paper. The help of Dr Karen Vukovič, Intern, is also much appreciated.

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Received 17 June 1986
Accepted 28 October 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp 596–597

Old abdominal burns and caesarean section. Case report

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Case report

At the age of 4 years the patient had sustained second- and third-degree burns of the lower abdomen, perineum and thighs, that resulted in severe scarring. She became pregnant for the first time at 24 years. Her pregnancy was uneventful until the 20th week. Thereafter, the patient suffered from mild dyspnoea. Lower abdomen distension did not occur and the enlarged uterus was displaced to the upper abdomen (Fig. 1), thus limiting respiratory movements. The patient had to reduce her housework, but hospitalization was not necessary. Fetal growth was normal at ultrasound examination and there were no signs of fetal distress; however, as the uterus could only expand transversely, fetal lie was transverse at term. Elective caesarean section was performed with a transverse incision in the lower uterine segment. As the bands of scar tissue were mainly longitudinal, a longitudinal incision of the abdominal wall was selected to avoid retraction of the incised scar and the need for a graft to close the wound. The abdominal muscles were involved in the dense scarring, and the bladder dome was displaced towards the umbilicus. The lower uterine segment was identified only after carefully mobilizing the bladder. A female infant was born, weighing 3100 g, who did well. The postoperative course was uneventful.

Discussion

The maternal and fetal hazards of burns in pregnancy have been repeatedly described, while only a few studies deal with old burns in pregnant patients (Matthews 1982).

It has been reported that abdominal scarring from old burns usually does not create problems during pregnancy, because the stretching capability of the scar tissue increases (Rai & Jackson 1975). Our patient confirms that uterine enlargement and fetal growth can be adequate in pregnant patients with old abdominal burns. Surgical release of the scar tissue during the second half of pregnancy has been described in patients with constrictive abdominal bands to relieve maternal pain. Our patient had no pain, but suffered from dyspnoea. Surgery was not attempted during pregnancy because abdominal decompression may precipitate labour (Haeseker & Green 1981) and the dyspnoea was not severe.

In contrast with other reports, vaginal delivery could not be accomplished because the uterine displacement caused fetal malpresentation. This complication does not seem to have been described before, even though Rai & Jackson (1975) reviewed 35 pregnancies occurring over an interval of 20 years. Vaginal delivery had been accomplished in most patients who had old or recent burns, and it was concluded that neither abdominal nor perineal burns prevent vaginal delivery. In our patient, fetal malpresentation associated with the scar tissue necessitating delivery by caesarean section.

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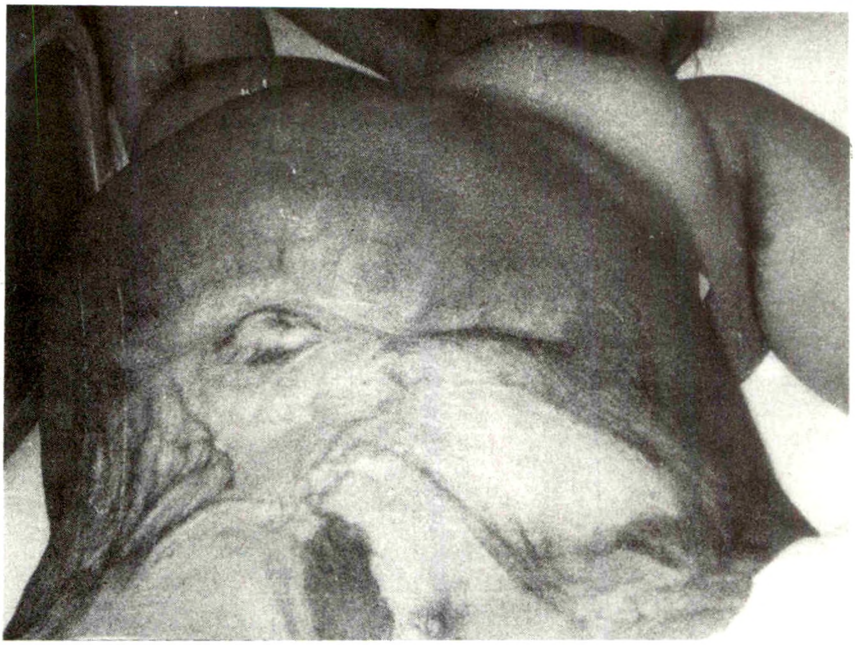

Fig. 1. Abdominal scarring at 28 weeks gestation.

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Received 14 April 1986
Accepted 8 July 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 598–599

Implantation of a cervical carcinoma in an episiotomy site. Case report

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Case report

A 33-year-old woman had been referred by her general practitioner with dyspareunia in October 1983. In March 1983, her first pregnancy had ended in the birth of a live boy by Kiellands forceps. Examination revealed the episiotomy scar to be well healed and not tender, and the cervix showed an erosion on the anterior lip. A Papanicolaou smear was performed using an Ayres spatula and slight contact bleeding was noticed. The smear was subsequently reported as showing occasional groups of malignant cells (grade 5 smear).

Colposcopy revealed the cervix to have a 'cauliflower-like' appearance with bizarre blood vessels showing a corkscrew appearance. Although colposcopically directed punch biopsy was reported as showing CIN 3 with possible microinvasion, an invasive lesion was strongly suspected. A large cone biopsy of the cervix was therefore performed under general anaesthesia. Microscopic examination of the removed cone of cervix showed an invasive squamous cell carcinoma, which extended to the lateral margin of the excision, the depth of invasion being greater than 5 mm. A diagnosis of Stage 1(B) carcinoma of cervix was thus made, as clinical examination in theatre had shown no spread to the vagina or parametrium. The patient was subsequently admitted again after the cone biopsy with vaginal bleeding, but this did not necessitate blood transfusion and settled without surgical interference.

In early January 1984 the patient was treated with radical radiotherapy. Over the course of 5 weeks, five courses of intracavity treatment were given using a cathetron, combined with external beam treatment over a 15 cm^2 field. There were no subsequent complications and in May 1984 a further cervical biopsy showed no evidence of residual tumour.

In September 1985 the patient noticed a swelling in the area of her previous episiotomy site. Clinical examination confirmed her findings, the lump measuring 4 × 3 × 3 cm and apparently arising in the episiotomy scar. Bimanual rectal and vaginal examinations revealed no obvious pelvic recurrence of the tumour. A CAT scan of the liver and pelvis was also negative. Excision biopsy of the lump was performed in October 1985. The lump was found to be infiltrating the connective tissue in the area of the previous episiotomy, but not the overlying skin, the vaginal wall or the rectum. Removal was incomplete. Microscopy of the tumour revealed an invasive squamous cell carcinoma.

In November 1985 an abdomino-perineal resection of the rectum was performed, removing the postero-lateral wall of the vagina and the residual tumour in the episiotomy site. A large defect in the perineum was left, which was closed as far as possible. An extra peritoneal end colostomy was sited in the left iliac fossa. The patient made an uneventful recovery and was discharged from hospital 16 days after surgery.

Macroscopic examination of the specimen revealed the excised rectum and anal canal to measure 24 cm. There was a firm white tumour measuring 3 × 1·5 × 1·5 cm in the perirectal fat above the anorectal junction. This protruded into the anal canal but the mucosa was intact. Microscopy revealed a poorly differentiated invasive squamous carcinoma with lymphatic involvement, consistent with the cervix as the primary site.

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Discussion

Carcinoma of the cervix is becoming increasingly common in younger women and death rates have doubled in women under 35 years of age in the last decade, although women under 35 years of age still only account for 6% of all deaths from cervical cancer (Draper & Cook 1983). Adelstein *et al.* (1981) also suggested a doubling in incidence of cervical cancer in women less than 35 years of age between 1969 and 1979, whilst figures from the Christie Radium Hospital, Manchester, suggested a 10-fold rise between 1965 and 1983. Obviously as these women are in the reproductive age groups, the diagnosis may be made during pregnancy or in the puerperium in some patients. La Vecchia *et al.* (1984) found that 9 of 103 patients below the age of 35 years with invasive cancer of the cervix were pregnant or less than 3 months postpartum at the time the diagnosis was made. Hacker *et al.* (1982) found a prevalence of cervical cancer of 1 in 2500 pregnancies. The situation is therefore not uncommon.

It is probable that our patient had an early invasive carcinoma of the cervix at the time of her delivery. Under these circumstances it seems likely that the cancer was transmitted down the vagina during the delivery, with subsequent implantation and growth in the episiotomy site. This area would be outside the subsequent field of radiotherapy. Kinch (1961) postulated that because of the potential risk of disseminating tumour cells, vaginal delivery should be avoided in women known to have cervical carcinoma. However, Shingleton & Orr (1983), reviewing the literature, concluded that maternal survival was not significantly affected by the mode of delivery and thought that the risk of tumour dissemination was more theoretical than real.

To our knowledge this is the first reported case of an implantation of a cervical cancer into an episiotomy site. Greenlee *et al.* (1981) reported a case of metastic nodules occurring in an anterior abdominal wall incision following a radical hysterectomy for a Stage I (B) carcinoma of the cervix. Thus it would seem that whether the patient is delivered vaginally or abdominally, implantation of the cancer is possible.

Careful follow-up of these patients is therefore recommended. The development of nodules in an episiotomy scar in women known to have had cervical cancer at the time of delivery is suspicious and early biopsy must be performed.

A cervical smear performed on this patient at her first antenatal clinic visit may have led to the earlier discovery of the cervical lesion and hence to earlier treatment. The importance of performing cervical cytology on antenatal patients is stressed.

Acknowledgments

We would like to thank Mr J. Harvey, Mr A. Roberts and Dr M. Adams for allowing us to report this case.

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Received 8 May 1986
Accepted 8 July 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 600–602

Intestinal heterotopia: an unusual cause of vulval ulceration. Case report

GARY YEOH, PATRICIA BANNATYNE, STEVEN KOSSARD, PETER RUSSELL

Case report

The patient, a 31-year-old white woman, was noted to have a small ulcer on a labium majus at a routine antenatal examination in the second trimester of her third pregnancy. On specific questioning, the patient conceded some slight irritation in the area for the preceding 'few months' but had not noticed any change in the skin. During this period, the lesion had persisted despite various self-prescribed topical medications and had recently become slightly painful during sexual intercourse and also on micturition. Consultation with a dermatologist was followed by an excision biopsy of a circumscribed ulcer measuring 7 × 6 mm with a soft reddened base. No other lesions were present on the vulva or perineum.

Pathology

Microscopically the central portion shows large bowel mucosa with focal erosions and a mild chronic inflammatory infiltrate (Fig. 1). The glands were straight, tubular and lined by goblet cells containing mucicarmine positive material and tall columnar cells some of which had brush borders along the luminal surface. Beneath the glands were small bundles of smooth muscle resembling splayed muscularis mucosae. Scattered through the muscle bundles were ganglion cells which appeared similar in arrangement to the submucosal plexus of Meissner (Fig. 2). There was a sharp transition at the edge of the lesion where the columnar cells abutted the normal squamous epithelium.

Comment

The expression of normal mature tissue in an abnormal site is known as heterotopia. Heterotopic intestinal tissue is not uncommon in the stomach and is occasionally seen in other parts of the gastrointestinal tract such as oesophagus, gall bladder (de Boer & Nairn 1972) and even in the tongue (Jankins 1969). By contrast, the presence of intestinal heterotopia beyond the gastrointestinal system is extremely rare; isolated reports note its presence in the renal pelves of kidneys showing chronic pyelonephritis or calculi (Salm 1969), bladder (Gordon 1963) and a urethral caruncle (Jarvi *et al.* 1984). The present case is, we believe, the first reported case of heterotopic colonic mucosa in the vulva.

The most common explanation for the replacement of one type of epithelium by another is simple metaplasia. This process can account for intestinal epithelium in oesophageal, gastric, gall bladder, renal and bladder mucosa and appears invariably to be associated with chronic irritation or inflammation. In many cases, the metaplastic epithelium is strikingly similar to normal intestinal mucosa and may even contain argentaffin or argyrophil cells and Paneth cells but is never associated with the appearance of a muscularis mucosae beneath the altered epithelium, as was noted in the present case. Although chronic irritation and inflammation are very common in the vulva, intestinal metaplasia is an unlikely reaction to it, given that the result is the emergence of an epithelium which is presumably more, rather than less, vulnerable to irritant factors.

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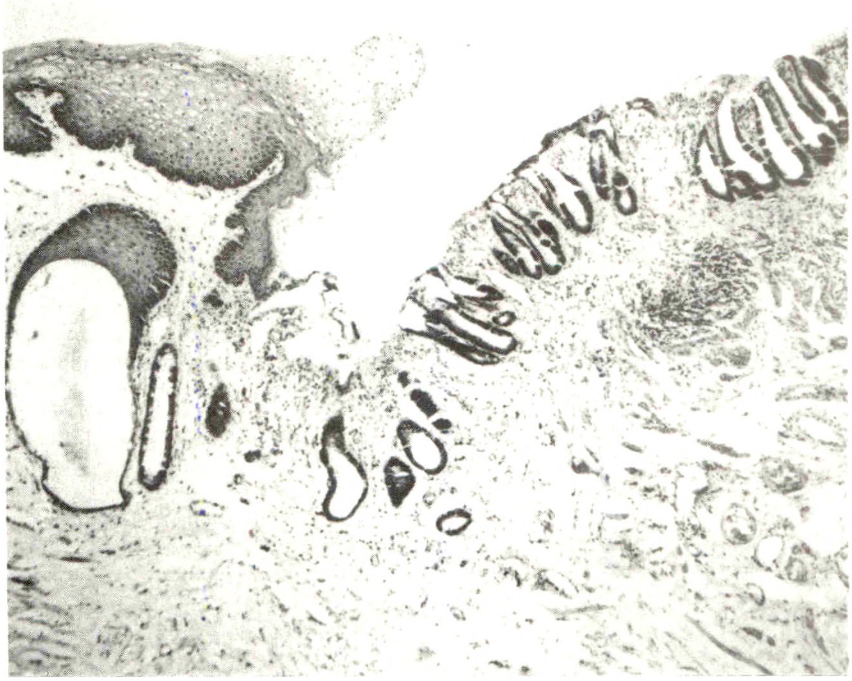

Fig. 1. Edge of vulval 'ulcer' showing an abrupt transition from normal keratinizing squamous epithelium to colonic type surface mucosa. Note the focal ulceration (centre) and patchy chronic inflammation in the lamina propria (centre right). Haematoxylin and eosin × 45.

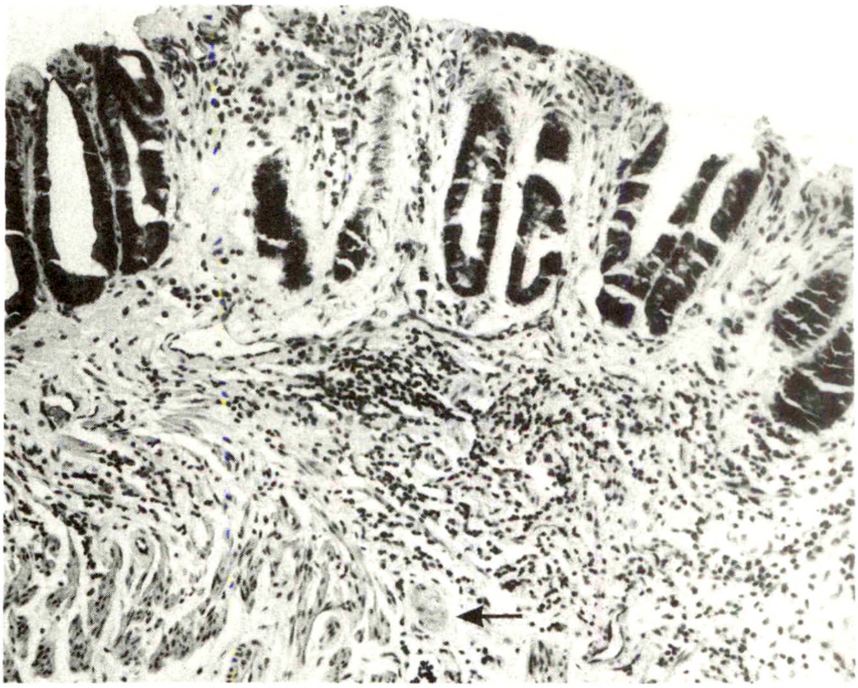

Fig. 2. Colonic heterotopia with well formed tubular glands, a lamina propria and a muscularis mucosae (lower left). The arrow marks the ganglion cell. Haematoxylin and eosin × 135.

Another explanation for tissue heterotopia in the vulva is a developmental aberration (dysontogenesis) resulting in the displacement of undifferentiated embryonic mucosa during the development and reshaping of the cloaca and the establishment of its external orifices. Such a process could result in the presence of a tissue which displays a more complex organized structure than expected with metaplasia. Displacement of undifferentiated stem cells which are later induced to develop into intestinal mucosa is an alternative related possibility.

The third explanation is that of implantation of intestinal mucosa into the vulva in postnatal life. Although implantation of squamous epithelium following trauma is well known, we know of no precedent for a similar phenomenon involving intestinal mucosa.

In assessing the merits of these proposed explanations it would be of some relevance to know the duration of the lesion in this patient. It is conceivable that a small focus of intestinal mucosa was present at birth, possibly enlarged during childhood, but became symptomatic only after a prolonged period of irritation in adulthood. We favour dysontogenesis as the basis of this previously unreported lesion.

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Received 25 June 1986
Accepted 27 August 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol 94, pp 603–605

SHORT COMMUNICATIONS

Transcutaneous electrical nerve stimulation in meralgia paraesthetica of pregnancy

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We describe three patients with severe meralgia paraesthetica in pregnancy who were treated successfully by transcutaneous electrical nerve stimulation (TENS), both to highlight the occasional severity of what is usually a minor problem and to provide the first description of the therapeutic benefit of TENS in this condition.

The women were 30, 31 and 37 years of age and developed meralgia paraesthetica between 25 and 30 weeks gestation in their second, fifth and second pregnancies respectively. One of the patients, who was walking with a limp and being kept awake at night by the pain, was actually admitted to hospital for neurological assessment. In one patient, the pain was exacerbated by the worry that these symptoms, which had occurred in two previous pregnancies and disappeared after miscarriages, heralded a third miscarriage. In all three patients, the pain had become a dominant feature in their lives and was sufficiently severe to provoke referral by the obstetricians to the Pain Relief Unit.

All three women were effectively treated by TENS with the 3M Tenzcare Pre-Set Stimulator Model 6215. The width and rate switches were set to deliver rectangular 200 μs pulses at a frequency of 100/s. Amplitude was variable between 0 and 85 mA as required by the patients to produce and maintain a strong but comfortable degree of paraesthesia at the site of stimulation. 3M Tenzcare disposable electrodes were placed on, or immediately adjacent to, the site of maximum pain in each case. Frequency and duration of use of the machine each day were varied as necessary by a patient to produce the desired degree of pain relief

Symptoms disappeared postpartum in all three patients.

Discussion

The subject of meralgia paraesthetica has recently been reviewed by Warfield (1986), and its association with pregnancy was described by Rhodes (1957). It is generally assumed that the syndrome is due to continual mechanical irritation of the lateral femoral cutaneous nerve somewhere in its course.

In meralgia paraesthetica of pregnancy, conservative measures are usually sufficient to treat the patient, consisting of reassurance that no harm is coming to the baby and that the symptoms will disappear after delivery.

Where symptoms are severe, physically disabling and detrimental to the woman's psychological well-being, more active measures are required. Since both the course of the nerve and the origin of symptoms may vary, the variable success rate of injection with local anaesthetic with or without steroid is not surprising. Surgery to attempt decompression, relocation or resection of the nerve is not warranted by a self-limiting condition. A technique is required which should bring a high success rate, be as non-invasive as possible and without effect on the fetus.

The principles and applications of TENS were reviewed by Woolf (1984) and Magora *et al.* (1978) described the successful treatment by TENS of pain arising from nerve compression injury.

The analgesic effect resulting from TENS arises principally at the segmental level of the cord receiving the stimulated afferents. Thus the stimulating electrodes require alignment somewhere over the course or distribution of the nerve innervating the painful area. It is not necessary to stimulate directly over the nerve lesion itself or proximal to the site of the pain. This is fortunate for the use of TENS in meralgia paraesthetica where the precise location of the

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nerve lesion is unknown, and reliable adhesion of electrodes in the groin may be difficult

In conclusion, meralgia paraesthetica is occasionally a severe, physically disabling, neurological complication of pregnancy which then warrants active management with a highly successful, non-invasive, non-neurolytic technique which does not carry fetal risk. Transcutaneous electrical nerve stimulation appears to be such a technique.

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Received 22 January 1987
Accepted 17 March 1987

Anti-cardiolipin antibodies and pre-eclampsia

Robert A. H. Scott *Medical Student, St Thomas' Hospital*

Theoretically, there appear to be many similarities between women with elevated antiphospholipid antibody levels (Hughes 1983; Harris *et al.* 1985) and pregnant women with pre-eclampsia. Both groups of women may develop placental infarction as a result of thrombosis of placental vessels, and in both groups prostacyclin levels appear to be low (Carreras & Vermylen 1982). It is noteworthy, too, that pregnant women with the lupus anticoagulant (an 'anti-phospholipid antibody') treated with steroids to prevent fetal loss develop symptoms like pre-eclampsia.

It appears possible that women presenting with pre-eclampsia may have elevated antiphospholipid antibodies. To test this hypothesis, I completed a study on a number of women in Ghana where there is a high incidence of pre-eclampsia.

Samples were taken over a 2-week period from 15 women, who had been admitted for pre-eclampsia to the Korle-Bu teaching hospital in Accra.

To account for local factors, this group of pre-eclamptics was compared with two control groups from the local population. One of the control groups comprised 40 women admitted to the hospital for surgery, who did not have a history of pre-eclampsia. The other control group comprised 25 pregnant women who were not pre-eclamptic.

The sera were frozen at −20°C and flown back to St Thomas' Hospital for assay, using the ELISA technique, to detect anti-cardiolipin antibody levels. The results of the tests are displayed in Fig. 1.

No significant difference was found between any of the sample groups and some positive results were found in both control groups. These elevated levels in some apparently normal patients may be due to malaria or other endemic infectious diseases. Only one woman had a level

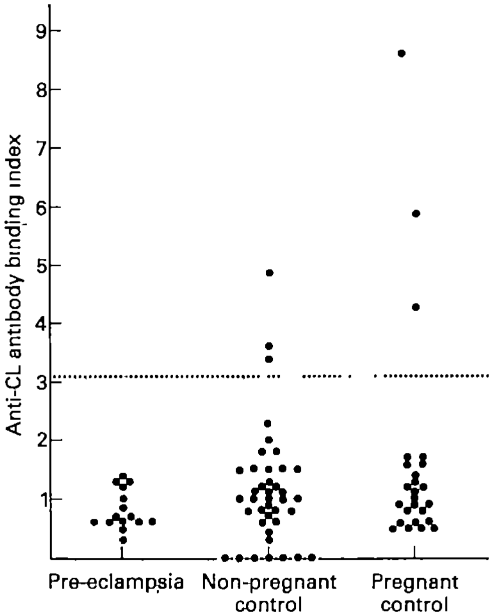

Fig. 1. Scatter diagram showing anti-cardiolipin (CL) antibody levels in the three groups of patients studied: women with pre-eclampsia, non-pregnant women; and pregnant women without pre-eclampsia. The interrupted line is the upper limit of normal.

Correspondence. St Thomas' House, Lambeth Palace Road, London SE1

of anti-cardiolipin antibody of a magnitude that might be associated with the anti-cardiolipin syndrome; she did not suffer from pre-eclampsia and it was possible that she was suffering from an autoimmune disorder like SLE, which is common amongst black populations.

The results showed no association between the anti-cardiolipin antibody and pre-eclampsia. Though women with the anti-cardiolipin antibody syndrome may be prone to pre-eclampsia, I could find no evidence to say that the converse might be true.

Acknowledgments

I thank Dr A. E. Gharavi and Mr T. Patterson for performing the ELISA tests and Dr E. N. Harris for his help in preparing the text.

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Received 3 June 1986
Accepted 6 August 1986

British Journal of Obstetrics and Gynaecology
June 1987, Vol. 94, pp. 606–608

BOOK REVIEWS

Issues in Reproductive Health Law in the Commonwealth by Rebecca J. Cook & Bernard M. Dickens. Available from the Publications Section, Commonwealth Secretariat, Marlborough House, Pall Mall, London SW1Y 5HX, 109 pages with figures and tables, £9.50

The argument that greater human suffering results from inadequate provision for maternal and child health services than from the conflicts created by military expenditure in a male-dominated world is very compelling, especially seen through women's eyes. The Commonwealth Secretariat presents periodic reviews of reproductive health laws for Ministers of 49 countries and their states with varying legal codes based largely on western culture. This Report, dealing with maternal risks, contraception, sterilization, abortion and infertility includes a review of the current status of the UN Convention on the Elimination of All Forms of Discrimination Against Women (CEDAW) or the 'Women's Convention'. With only 14 years to run before those countries bound to CEDAW must achieve equality between the sexes, 21 Commonwealth countries have so far ratified or acceded and another four have only signed. Canada has given the principal lead, and it is no coincidence that this very clear and detailed analysis of Commonwealth law carries the North American imprint of its authors.

Assertion and acceptance of women's rights has been the major social theme of our generation and no branch of medicine has been more involved in that movement than obstetrics and gynaecology. Progress in what laws compel and what doctors do has shown leadership mainly from the latter. Yet two-thirds of the world's neonates are delivered into the hands of Traditional Birth Attendants, and infant mortality in the mid-80s is still 18 times greater in Sierra Leone than the UK or Australia. A growing number of UK students and doctors are becoming familiar with the realities of health budgets in developing countries and the prime importance of maternal and child health programmes—circumstances which surround the lives of a large proportion of the College's membership.

Much of the Report deals with the growth of case laws in the field of fertility, and the ways in which these are applied differently (sometimes fallaciously) throughout the Commonwealth. Bourne on abortion, Bolam on consent to treatment, Gillick on mature minors are examples of international significance fully explained in a text that is remarkably warm and compassionate. There is invaluable detail concerning the development of the legal framework surrounding sterilization in all circumstances, its failure, and the nature of consent and spousal veto. The differences in abortion law are tabulated, and the wider implications of contraception and adolescent maternity in such countries as Nigeria where one quarter of women are married by the age of 14, and half by 16, are clearly set out. There are basic differences in laws about the duty of doctors to inform their patients; in Canada the standard is that of the objective patient rather than what the doctor's peers would do.

The Report is a major service to jurists, policy-makers, politicians and demographers. It should be found in every library used by members of our speciality, and those who are drawn into its easy typescript and lightly legal terminology will find a fascinating account of the legal standing of women's rights and dignity in health across a world of nations which the College itself represents in its wide Commonwealth membership and influence. At the very least we can read what is being told to Ministers of Law, Health, and those responsible for women's affairs and judge these politicians by their responses.

Anthony Alment

Perinatal Medicine: Problems and Controversies edited by G. C. Di Renzo & D. F. Hawkins. Cortina International, Verona, Raven Press, New York, 1986, 221 pages with figures and tables, £38.50

Contact between English obstetricians and their counterparts in mainland Europe is still poor, and 'British-Italian co-productions' are more common in the world of movies than that of obstetric textbooks. This is perhaps surprising because Italian universities are among the oldest in the world and at least one British medical school was founded by graduates from Italy. 'Perinatal Medicine' is co-edited by obstetricians from Perugia and Hammersmith and is a remarkable tribute to the late Giorgio Montanari, who was successively professor of obstetrics and gynaecology at Padua, Turin, Messina and Modena, and who died in 1981 at the early age of 52. The editors have invited 35 contributions from authorities in the USA, England, Italy and several other European countries. Contributions are arranged in four groups: on the monitoring of pregnancy, assessment of fetal lung maturity, preterm labour and psychosomatic factors in perinatal medicine. Topics range from drug addiction to predicting pregnancy-induced hypertension, and among the necessary but predictable subjects—cardiotography, pH measurement, surfactant production, tocolysis, and mode of delivery of the preterm baby—there is the pleasure of the unexpected: fetal electroencephalography, sonic stimulation, intrauterine surgery and the endocrine response to stress in labour. Some contributions, such as the chapter on 'fear of childbirth', are research papers and others, such as Professor Eskes' Dutch perspective on 'home versus hospital', are scholarly reviews, but in the section on preterm labour all the contributors do their best to give practical advice on difficult clinical problems. The book is in English, the new lingua franca of science, and the great majority of references are to English-language journals. It is edited to a very high standard and is as readable as a collection of reviews from the sharp end of medicine can be. One does rather wonder who will have the time and the academic inclination to sit at the fireside or on the patio and read three dozen state-of-the-art reviews on such a variety of topics, but if there are perinatological renaissance men, this is their ideal companion.

J. O. Drife

Reproductive Failure edited by Alan H. de Cherney. Churchill Livingstone, Edinburgh, 1986, 308 pages with figures and tables, £39.00

The Editor of this new volume on infertility issues a challenge to reviewers with the opening statement of his preface: 'This text should become the standard by which other books about infertility, early pregnancy wastage, and other clinical problems of reproduction are measured'. In addition he claims to have gathered together *the* leading experts in their individual fields, when 13 of 16 authors come from the United States and the remaining three from Israel. I addressed the book, therefore, with some misgivings, but was pleasantly surprised to find that these were quickly dispelled. In so far as a single text can cover all different aspects of reproductive failure I think this book does present an overview of the state of the art. In addition it is eminently readable with clear illustrations and ample references. I found the introductory historical chapter by Professor de Cherney fascinating and having started it on the train almost went through my station. In addition to the common aspects of infertility, there are interesting chapters on human sexuality, infection, immunologic factors and habitual abortion. The general approach is extremely practical with excellent guidance on the management of patients and the execution of laboratory, clinical and surgical procedures as well as very useful reviews of the literature relating to outcomes. There are of course many recent specialized texts covering particular areas, such as in-vitro fertilization, but this work should be extremely valuable both to practitioners training in reproductive medicine and to those who wish to bring themselves up to date with current technology and practice. It can be highly recommended.

R. S. Sawers

Books received some of which may be reviewed at a later date

The Foetus as Transplant Donor: Scientific, Social and Ethical Perspectives by Peter McCullagh. John Wiley & Sons, Chichester, 1987, 215 pages with figures and tables, £25.00

Radiation Therapy and Gynecological Cancer edited by Dattatreyudu Nori & Basil S. Hilaris. Alan R. Liss, Inc., New York, 1987, 444 pages with figures and tables, £47.00

High-Risk Pregnancy: A Team Approach edited by Robert A. Knuppel & Joan E. Drukker. W. B. Saunders Company, Philadelphia, London, 1986, 604 pages with figures and tables, £29.50

Baillière's Clinical Endocrinology and Metabolism: International Practice and Research (Reproductive Endocrinology Vol 1, No 1) edited by H. G. Burger. Baillière Tindall, London, Philadelphia, 1987, 246 pages with figures and tables, £15.00 (UK and Eire), $25.00 (USA & Canada) and £18.50 (all other areas)

Bladder Reconstruction and Continent Urinary Diversion edited by Lowell B. King, Anthony R. Stone & George D. Webster. Year Book Medical Publishers Inc., Chicago, London, 1986, 379 pages with figures and tables, £62.00

Current Reviews in Obstetrics and Gynaecology Vol 12, Endometriosis edited by Daniel T. O'Connor. Churchill Livingstone, Edinburgh, 1987, 154 pages with figures and tables, £18.00

Clinics in Obstetrics and Gynaecology Vol 13, No. 3, The Human Placenta edited by Tim Chard. W. B. Saunders Company, London, Philadelphia, 1986, 421–663 pages with figures and tables, £13.50

Management of Ovarian Cancer edited by G. Blackledge & K. K. Chan. Butterworths, London, 1986, 214 pages illustrated, £40.00

A Colour Atlas of Gynaecological Surgery, Vol 1, Vaginal Operations Revised Edition by David H. Lees & Albert Singer. Year Book Medical Publishers Ltd, London, 1987, 222 pages, fully illustrated, £60.00

Proceedings and Symposiums

Fetal Physiological Measurements 342 pages with figures and tables, £50.00, and **Neonatal Physiological Measurements** 476 pages with figures and tables, £45.00. Both books cover Proceedings of the Second International Conference in Fetal and Neonatal Physiological Measurements Oxford, 1984 edited by Peter Rolfe, Butterworths, London, 1986.

The Computer in Obstetrics and Gynaecology (based on a conference of the same name held at Cambridge, 1986) edited by Kevin J. Dalton & Rupert Fawdry, IRL Press, Washington DC, 1987, 234 pages, £30.00, US $54.00

Genetic Aspects of Developmental Pathology March of Dimes Birth Defects Foundation, Vol 23, No. 1, 1987 (Solicited papers and proceedings of a Symposium in Madison, Wisconsin, 1985) edited by Enid F. Gilbert & John M. Opitz. Alan R. Liss, Inc., New York, 1987, 522 pages with figures and tables, £84.00

Prenatal Diagnosis of Heritable Skin Diseases Volume 16: Current Problems in Dermatology (35th Annual Symposium on the Biology of the Skin, Oregon, 1985, and European Society for Dermatological Research Clinically Orientated International Symposium, Oslo, 1986, edited by T. Gedde-Dahl Jr & K. D. Wuepper. Karger, Basel, 1987, 216 pages with figures and tables, SwFr 218, DM 261, £99.10, US $121.25

Erratum

Br J Obstet Gynaecol **94**, 94

Book reviews. Surgery of Female Incontinence second edition edited by Stuart L. Stanton & Emil Tanagho. Springer-Verlag, Berlin

Paragraph four should read 'Voiding difficulty is not uncommon after bladder neck surgery . . .' and **not** 'now uncommon' as printed.

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Edited by **Madeleine H. Shearer** RPT

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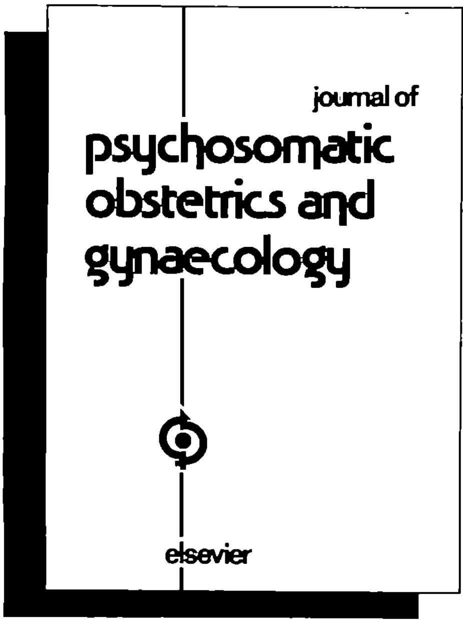

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Altman, D G , Gore, S M , Gardner, M J & Pocock, S J (1983) Statistical guidelines for contributors to medical journals *Br Med J* **286,** 1489–1493

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Hytten, F E & Leitch, I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p 26

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Volume 94, Number 7, July 1987

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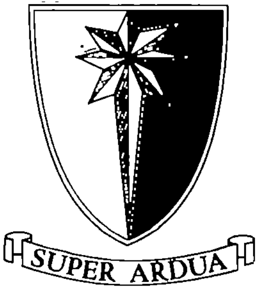
British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten



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BJOGAS 94(7) 609–720 1987 ISSN 0306-5456

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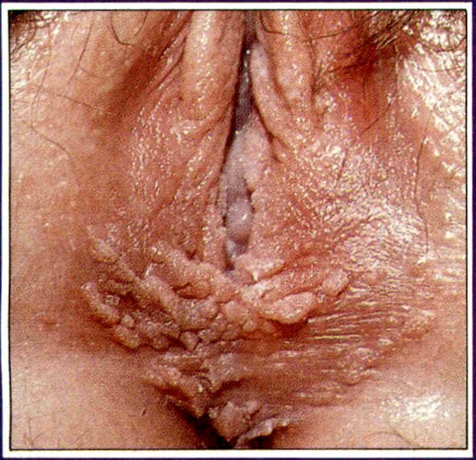

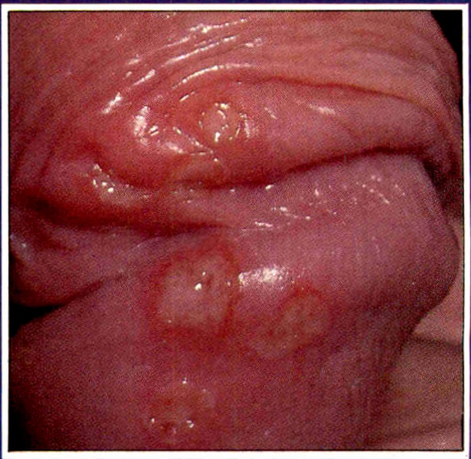

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79, **301,** 677. 2. Richardson,J.A. & Dixon,G., *Brit.Med.J.*, 1976, **1,**
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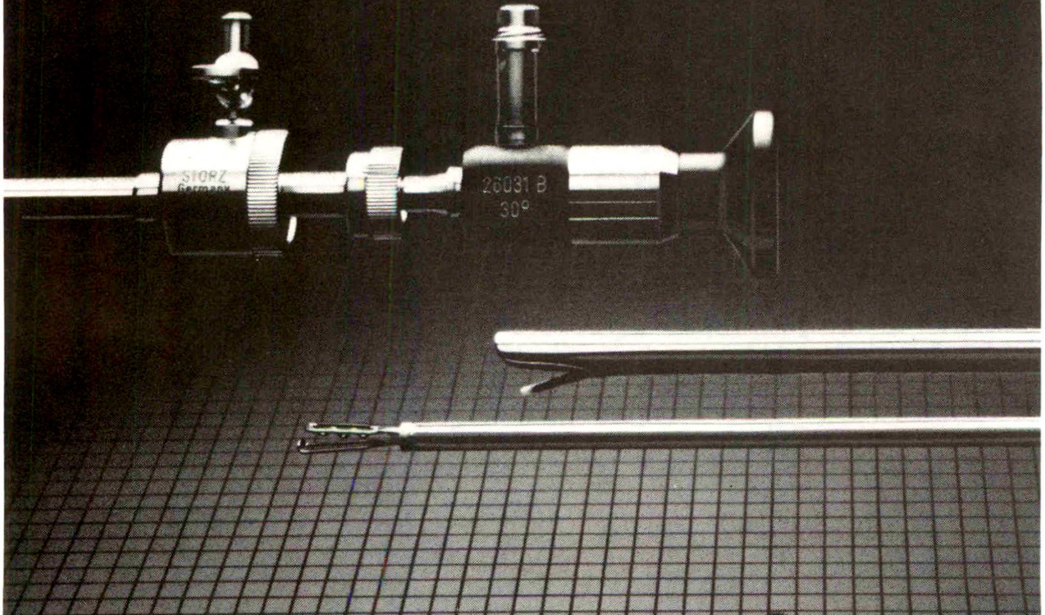

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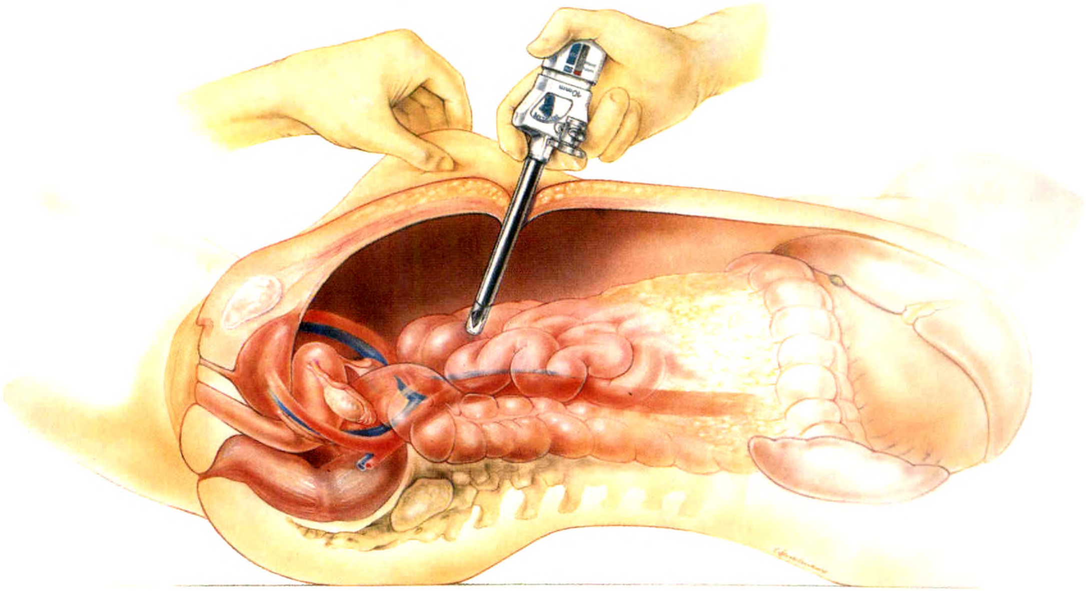

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COMMENTARY

In whose interest is access to medical records withheld?

There is continuing debate about the rights of individuals to have access to personal information about themselves kept on file by officialdom. At present, the secrets kept from the public by government, local authorities, the law and the health service include records about housing, education, employment, social work, parole and probation and files about pensions, benefits and medical care. A public opinion poll carried out by MORI for the Campaign for Freedom of Information shows that the majority favoured access to national insurance and social security records and the right to see records kept by banks, building societies and employers. Seventy-three percent of those questioned wanted access to their own medical records.

In September, 1987, members of the public will have the right to read their own medical notes if those records are held on a computer. Logically, they might then expect those rights to be extended to ordinary case notes. However, exemption from access has already been granted for eight types of computerized record, such as data to which professional privilege, as between lawyer and client, could be claimed. At the time of writing, the Government still has to decide to what extent to exempt data on physical or mental health. In June 1986, the BMA voted for medical records being included in such exemption on the basis that having such information was not in patients' best interests.

There have been a number of studies in which doctors have analysed the content of medical case notes in an attempt to assess the advisability of allowing patient access (Short 1986; Sergeant 1986). Among reasons given for withholding access to case notes is the presence in them of material unsuitable for patients to read, including comments and remarks of a personal nature. Sergeant (1986) considered that going through the records removing 'hurtful statements from the thoughtful but bulky records would need time and sensibility' and argued that omitting sensitive information creates difficulties, and thus restricting access is the only solution. As pointed out elsewhere (Elbourne & Lovell 1986), a rather different interpretation and different lessons could be learned from the same data. Perhaps what these studies have revealed is the need to improve the quality of record-keeping in the future, including the avoidance of litiginous remarks, rather than using the present content of case records as justification for continued lack of access to them by those whom they concern most personally.

In a number of Commonwealth countries, the USA, in many European and in some Third World countries, people are accustomed to being given their own medical records. In this country, experiments have shown the success of allowing access to records, for instance, where parents hold their child's health records (Greene & Macfarlane 1985). In a general practice context, Bird & Walji (1986) report the positive effects of allowing patients access to their own medical records. Baldry *et al.* (1986) found that 12% of the patients surveyed had discovered inaccuracies ranging from wrong addresses to an incorrect note that a termination of pregnancy had taken place. Worryingly, they also noted that only a small number of these patients then dared to point out these errors to the health professionals!

It is in the obstetric field that this practice has been tried and shown to be feasible in a number of centres. In Bradford, women have been carrying their own obstetric records since 1968 (Wilton 1983). This policy has been tried and reported as successful in Portsmouth (Murray & Topley 1974), Oxford (Bull 1983), Lambeth (Zander *et al.* 1978) and Cambridge (Draper *et al.* 1986). The existing evidence suggests that users of services want to have access to their own records while professional views about it tend to be mixed; concern often being expressed based on the wish to protect the patient.

Interestingly, on the one hand, the debate about access to obstetric records generates considerable heat in the medical profession while at the same time, it is also seen as a trivial issue and some journals are unwilling to give much space to it. When being interviewed during the St Thomas' Maternity Case Notes Study, a senior registrar remarked that researching the effects of access to obstetric records was 'of no interest to obstetricians' (Lovell *et al.* 1986).

The anxieties and ambivalence of the professionals are vividly demonstrated by the findings reported in the randomized controlled trial carried out in Newbury, West Berkshire. The experimental group of expectant mothers who took part in the study were given their own obstetric records while the control group carried a co-operation card and their main records were held by the hospital. All women obligingly filled in four questionnaires and clearly welcomed the interest shown in their views (Elbourne 1987). In spite of misgivings displayed by some of the local doctors, nothing untoward happened. The experimental women clearly liked having their own records and the controls would have enjoyed the same privilege because when both groups were asked which record they would opt for on a future occasion, holding case notes was the preference in both ($P<0{\cdot}01$).

The findings in Newbury, a predominantly middle class area in rural Berkshire, were in fact very similar to the results of our own study in Lambeth, an inner city area. The women who carried their notes felt more in control and said they found it easier to talk to the health professionals looking after them.

Perhaps the most important positive effect of giving pregnant women their own notes to carry in the Lambeth study was that the records were much more accessible to everyone—the usual frustrations and time wasting exercise of hunting for notes, as well as the distress caused to the women, were avoided. In Newbury, these positive effects were not so dramatic but notes were certainly no less accessible than when held by the medical records department. When women carry their own notes they usually do not lose them. This saves clerical and medical time as well as time filing and retrieving notes, even when they are not mislaid.

As can be seen by inspection of the results in the article by Elbourne and her colleagues in this issue (p. 612), carrying notes makes little difference to smoking and drinking behaviour but the potential of the notes as a health education tool is undoubtedly there. What seems to have emerged from this study (and the work at St Thomas') is that giving women their own obstetric notes is a good idea *as far as it goes.* Providers of obstetric care and users *both* need to be properly briefed about the use of the notes so that the maximum benefit can be achieved. The notes might also usefully be redesigned to include space for the woman herself to note down questions and issues which she wishes to discuss and perhaps a birth plan. In this way, the notes might provide even more of a focus for discussion with both sides reading the input of the other.

Currently, health education tends to be perceived in the limited terms of professionals educating the users of services. Pregnancy, labour and childbirth are usually normal processes but have emotional as well as physical outcomes. The hospice movement has successfully encouraged more openness and the aim of 'death with dignity' as every person's right. At the other end of the life cycle, 'birth with dignity' should also be achievable. The ways that this is to be accomplished include the pregnant woman being able to make certain choices and direct the course of events. She cannot do this without informing her carers about how she wants things to be done, and she is not in a position to make informed choices without knowing what is and is not available and without possession of all the relevant information concerned with her own and her baby's health, health care and services provided by the institution and its workers. This means health education in the broadest sense: a two-way exchange of information—from the mother to her carers and from the carers to her.

How is the experiment of allowing women to carry their own notes to be assessed? What outcomes are to be used in order to describe the new policy as *'successful'?* In other words, success according to whom?

In the interests of both users and providers of services clinical safety is paramount. For this reason, research studies measure clinical outcomes. In none of the relevant (but admittedly small) studies was there any suggestion that carrying the obstetric notes had any adverse effect on the health and safety of the woman or her baby.

Administratively, it was shown beyond doubt that a system of patient-held records saved clerical and clinical time and did not result in a decrease in the availability of notes.

Would carrying their own notes encourage women to behave in a healthier way? Would they smoke and drink less? Would they attend classes and clinics and be more likely to breastfeed? Carrying their own notes did not appear to have any effects on these aspects of behaviour. Most women complied whether they had their own notes or not.

Satisfaction of the women was also measured and significant differences between the control and experimental groups were not detected unless we take into account the strong preference expressed for carrying notes. Women want to carry their own obstetric records. Is 'wanting' enough to make it in their own best interest? Women also said that having their own notes made them feel 'more in control'. Control is related to power and what has thus far been left out of this discussion is the role of *power*. Doctors are claiming that they know what is best for their patients and, with this in mind, insist that they wish to protect their patients by limiting their access to case notes. In order to protect, it is necessary to have power. Perhaps we should be more questioning and as Ian Kennedy tellingly asked in his Reith lectures: 'Who invested doctors with such power'? (Kennedy 1981). Waitzkin (1979) goes so far as to suggest that the power relation between doctor and patient is so uneven that 'doctors and patients inhabit different social worlds'. When the women in the Elbourne study said that they 'felt more in control', this might be a small step towards shifting the balance of power. Possession of knowledge and information are vital if the relation is to become more equal.

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British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 612–619

The Newbury Maternity Care Study: a randomized controlled trial to assess a policy of women holding their own obstetric records

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Summary. To assess a policy of women holding and thus having constant access to their own obstetric records, 290 women attending a peripheral consultant clinic in Newbury, West Berkshire, were randomly allocated to hold either their full case notes, or the more usual co-operation card. Women holding their full records were significantly more likely to feel in control of their antenatal care (rate ratio 1·45; 95% confidence interval 1·08–1·95) and to feel it was easier to talk to doctors and midwives (rate ratio 1·73; 95% confidence interval 1·16–2·59). No other beneficial effects were detected. Asked about their preferences for any subsequent pregnancies, women holding their own records in the index pregnancy were more likely to say they would prefer to hold the same kind of record again in a subsequent pregnancy than were women holding a co-operation card (rate ratio 1·56; 95% confidence interval 1·34–1·81). There was no evidence of negative effects. In particular, women holding their case notes did not feel more anxious than co-operation card holders. The policy of women holding their notes resulted in savings in clerical time, without evidence of an increase in the rate of lost notes.

The present system of shared maternity care in the United Kingdom is characterized by multiple contacts between women and a variety of staff. This situation has spawned a number of parallel medical records systems. At a minimum these include those of hospital staff, the woman's general practitioner and the community midwife. This duplication may be wasteful of scarce resources—particularly time. The system of multiple records may also contribute to poor communication between the different staff groups. The use of co-operation cards, which were introduced in an attempt to facilitate liaison between staff (Hamilton 1956), means that at least two records always have to be completed. Unlike the other records, however, these cards are seen and held by the women concerned. This provides a precedent for introducing a system of medical records in which the woman sees and holds the only record of her obstetric care.

In England, a recent survey of midwifery policies and practices (Garcia *et al.* 1986) suggests that out of 193 health districts, over 40 (20%) already have (or are planning to introduce) a system which includes records held by women using the maternity services.

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Previously published reports from five centres [Bradford (Wilton 1983); Portsmouth (Murray & Topley 1974); Oxford (Bull 1983); Lambeth (Zander 1982) and Cambridge (Draper *et al.* 1986)] have provided considerable evidence about the feasibility of a system in which the only set of obstetric records is held by the woman. Benefits in terms of women feeling better informed and more involved in their care, and savings in clerical time were noted in these areas. In contrast, other writers have expressed fears that notes would be lost and patients would be made anxious by reading the contents of their records (Ross 1986; Short 1986). All the published studies, however, suffer from methodological weaknesses including either the lack of any control group, or controls who were not randomly selected.

A proposed change in the maternity records system in the West Berkshire health district provided an opportunity to mount a randomized controlled trial to compare the effects of policies whereby women do, and do not, hold (and therefore have constant access to) their full obstetric record.

Hypotheses

Specific hypotheses were formulated in terms of women's feelings and behaviour, and of administrative efficiency. Some of these hypotheses were derived from previous studies about women holding their maternity records (Wilton 1983; Murray & Topley 1974; Bull 1983; Zander 1982; Draper 1986). Other hypotheses were drawn from a trial which demonstrated that women receiving a high level of feedback about the findings of ultrasound scans in early pregnancy reported fewer worries, more confidence, and were more likely to reduce their smoking levels than controls to whom minimal feedback had been given (Reading & Cox 1982). Research into effects of social support in pregnancy and early parenthood suggested further hypotheses about women's feelings and health related behaviour (Carpenter *et al.* 1968; Gutelius *et al.* 1977; Larson 1980, Carter-Jessop 1981; Oakley *et al.* 1986).

Using these and other studies, it was hypothesised, firstly that, compared to women whose notes remain in the care of the maternity services, women holding their own obstetric records would be more satisfied with their maternity care. Secondly, it was hypothesised that concerning the pregnancy, they would feel better informed, less anxious, more confident, and more in control and that the baby's father was more involved in the pregnancy, labour and the care of the child. Thirdly it was hypothesised that they would be less likely to suffer from depression and would find it easier to communicate with staff in the maternity and child services. Lastly it was also hypothesised that these women would smoke fewer cigarettes, attend more frequently for antenatal care, be more likely to attend antenatal classes, have shorter labours, have less analgesia or anaesthesia, be more likely to have spontaneous deliveries, be more likely to attend well-baby clinics and be more likely to breast-feed.

On the administrative side it was hypothesised that, compared to a system of centrally-held records, a system of patient-held records would result in an increase in the availability of notes and a saving of clerical resources.

In general, these hypotheses have been expressed in terms of a direction of difference, but have not been expressed quantitatively due to a dearth of information on which to base such estimates.

Subjects and methods

Background

Most women resident in the West Berkshire health district are booked for shared or consultant-only care and are delivered in the Royal Berkshire Hospital in Reading. There are also some births in general practitioner units such as the Sandleford Hospital in Newbury, a small town in a predominantly rural area, about 20 miles from Reading. Antenatal care is provided either at the Royal Berkshire Hospital, in peripheral consultant clinics (including Sandleford Hospital), in health centres and general practitioner surgeries, occasionally at home, or in some combination of these alternatives. Before 1984, the consultant obstetric case notes were held centrally at the Royal Berkshire Hospital. Individual general practitioners and midwives kept their own records, and liaison was provided by the co-operation cards held by women. From January 1984, two of the four consultant obstetricians continued with this system. Nearly all the women under the care of the other two consultants held their full obstetric record for the index pregnancy. (Basic identifying details and past obstetric records were still held in the medical records department in Reading). However, for a trial period of 6 months, a randomly selected half of the women booking under the care of one of us (E.H.) at the peripheral clinic in Newbury held co-operation cards instead.

Ethical considerations

The research was approved by the ethics committee of the West Berkshire Health District

Sample size

The results of a comparable study (Klein *et al.* 1985), using a five-point scale as an indicator of satisfaction with care, suggest that an overall sample size of 280 would provide an 80% chance of detecting an effect of the order of 0·43 (one third of the standard deviation) on such satisfaction at the 5% level of statistical significance. The ultrasound study by Reading & Cox (1982) detected several clinically relevant and statistically significant differences with a sample size of less than 140.

In practice, the sample size was constrained by the size of the Newbury clinic and the period of time available for recruitment (6 months).

Eligibility

All women less than 34 weeks gestation who booked for antenatal care with E.H. at the peripheral clinic at the Sandleford Hospital, Newbury, between 1 January and 30 June 1984 were considered eligible for entry into the trial.

Allocation

At the time when the midwives first contacted the antenatal clinic clerk to initiate the process of maternity care, 317 women were randomly allocated (by D.E. and M.R. using a consecutively numbered series of sealed, opaque envelopes) to one of two policies: either (i) to hold their own obstetric case notes until 10 days after delivery ($n = 161$) or (ii) to hold a co-operation card while their case notes were held by the medical records department ($n = 156$). Twenty-seven of these 317 women were found not to be eligible for entry into the trial because, for example, they were booked for general practitioner-only care, or for care under a different consultant. The two allocated groups were very similar both in terms of the overall proportion considered ineligible, and in terms of the specific reasons for their ineligibility. After they had been informed about the trial and given their consent, the 290 eligible women began their involvement in the study by accepting a questionnaire given to them by the community midwife after she had recorded their booking history.

Data sources

Information about women's attitudes and behaviour was obtained from self-administered, mainly precoded, postal questionnaires completed at four points in time—when the booking history was recorded; at about 34 weeks gestation; 10 days postpartum; and finally at 6 months postpartum. In order to provide an objective check on women's reported smoking behaviour, 5 ml of urine were collected from the samples they provided routinely at around 34 weeks gestation, then 'pooled' into two containers (one for each randomly allocated group), and sent for cotinine assay (Peto 1983; Jarvis *et al.* 1984; Woodward *et al.* 1984; Etzel *et al.* 1985). Additional clinical information was extracted from co-operation cards and case notes. Information about administrative effects was derived from observations in medical records departments, supplemented by informal interviews with relevant staff.

Questionnaire response rates were very high Out of the 147 eligible women allocated to hold case notes and the 143 allocated to hold co-operation cards, there were only two outright refusals. Both of these were from women allocated to hold co-operation cards and for reasons unconnected with the study. In the first week after recruitment, three women suffered miscarriages and one had the pregnancy terminated, and so did not complete their first questionnaires. No further questionnaires were mailed to these six women, nor to the 13 women who later suffered a spontaneous or induced abortion (9), stillbirth (1) or neonatal death (3), nor to one women who emigrated. (One of the mothers whose baby died in the neonatal period was interviewed at home by D.E.). It was decided not to send the third questionnaire to two women in the light of serious neonatal and maternal morbidity.

Several women who had not replied to one of the earlier questionnaires (usually because of change of address or preterm delivery) did send back later questionnaires. By the time of the final questionnaire (approximately a year after the first), the number of respondents was 128 in the case-note group and 119 in the co-operation card group—92% of those mailed (or 85% of the 290 originally recruited into the study). There was a tendency for the response rate to be slightly higher in the case-note group, but the differences could easily be explained by chance.

At the time of booking, all but three women had received the type of records to which they had been randomly allocated. One woman in the case-note group had psychiatric problems including periods of amnesia and decided in consultation with her doctor that it would be better if her notes were held by those caring for her. Two women in the co-operation card group held their notes, one because of an extra antenatal visit in Reading (where she was given her notes because all E.H.'s patients there were note-holders), and the other because of a midwife error. In addition, there were at least 10 women whose actual record holding differed from their allocation at some later stage between booking and the end of their maternity care. This was mainly because they moved from the area and as women in most other areas do not hold notes, it is likely that most of these movers would have held co-operation cards.

Statistical methods

The two randomized groups were compared either in terms of rate ratios and their 95% confidence intervals (Miettinen 1976) or means and *t*-tests, where appropriate. In general, a confidence interval including unity suggests no statistically significant difference between the policies; values above unity suggest a benefit of holding case notes, and values below unity suggest an adverse effect. Calculations were performed using SPSS-X (SPSS 1983) on the Oxford University ICL 2988 mainframe computer, or the Hewlett Packard HP-41 programmable hand calculator (Rothman & Boice 1982).

Results

Comparability

The two randomly generated groups of women were comparable in terms of their sociodemographic characteristics (such as age, marital status, social class and parity) and their smoking behaviour at recruitment to the trial. They were also very similar in terms of their answers to the socio-psychological questions in the recruitment questionnaire. These included their feelings about their physical well-being, happiness, general and specific anxieties, general and specific confidence, and the feelings of the baby's father towards the pregnancy.

Women's attitudes and behaviour

Two of the hypotheses about the effects of the intervention on women's feelings were supported. Women carrying their own notes were nearly one and a half times more likely to say they felt more in control of their pregnancies (rate ratio 1·45; 95% confidence interval 1·08–1·95) and more than one and a half times more likely to say they found it easier to talk to the doctors and midwives antenatally (rate ratio 1·73; 95% confidence interval 1·16–2·59) than women holding only co-operation cards. These beneficial effects were observed in spite of a tendency for women holding their case notes to feel it was more difficult to understand (and read) what was written in them than women holding co-operation cards. There were no statistically significant differences overall between the groups in terms of the women's feelings of being well informed, anxious, confident, depressed, satisfied with their care or about involvement by the baby's father. Nor were there statistically significant differences between the groups in terms of 'within person' changes in anxiety and confidence over time. Similarly, clinical outcomes and women's health-related behaviour did not exhibit statistically significant differences either between the two groups overall, or in terms of 'within-person' changes over the time period in the number of cigarettes smoked.

Asked about which type of record (case notes or co-operation card) they would prefer to have if they were to become pregnant again, women showed a tendency to prefer the record with which they were already familiar. However, this tendency was significantly greater for women holding their case notes (rate ratio 1·55; 95% confidence interval 1·34–1·81). Just over half the women allocated to hold co-operation cards (58%) expressed a wish to have a co-operation card in their next pregnancy. In contrast, nearly all the women allocated to hold their case notes

(91%) wished to hold their full record in their next pregnancy.

The availability of records

There was no evidence that a policy of women-held notes increased the availability of case notes in antenatal clinics. Staff recorded 11 occasions (4% of women in the trial) in which notes were not available at antenatal clinics. This percentage was the same whether the notes had been forgotten by women who were holding them, or whether they had not been sent from the medical records department for women holding co-operation cards.

Clerical resources

The main saving in clerical resources emanating from a system in which women held their own records was a reduction in the time spent by medical records clerks retrieving notes from and returning them to a central filing system. Observations on two separate occasions in the maternity records office in Reading suggested that the task of pulling and refiling case notes (and hence the potential for time saving) was approximately 3 min per set of case notes. In practice, because the consultants of women carrying their own notes requested the notes relating to previous pregnancies, very little time was actually saved in Reading. In the peripheral clinic in Newbury approximately 1 h/week was saved. This ensured that the part-time clinic clerk could complete her job within the hours she was paid to work rather than, as often happened, during unpaid overtime. Clinical time was saved by elminating the need to write duplicate notes, for instance, in the full medical record and the co-operation card.

Discussion

The Newbury Maternity Care Study has demonstrated advantages (women's feelings of greater control over their antenatal care and of greater ease in talking with doctors and midwives) of a policy of women holding their full obstetric records rather than a co-operation card. This experimental policy also resulted in savings in clerical time. The disadvantages feared by some before the trial—that women would lose their notes, or would be made unnecessarily anxious—did not materialize. From the women's comments, the difficulties in understanding the notes related more to their legibility, as also found by Draper (1986), than their content.

These results are consistent with those of the other studies in the maternity field. However, it is clear from this and two other studies using a control group [Draper *et al.* (1986) in Cambridge; Lovell *et al.* (1986) at St Thomas' Hospital in London] that the size of the effects, while both important and statistically significant, are not as large as some protagonists of women holding case notes have suggested. This may be related to the research design: women in the control group may have been indirectly exposed to the experimental policy through the attitudes of staff who participated in both systems, and through contact with women who were carrying their notes ('contamination'). In the St Thomas' study (Lovell *et al.* 1986) the control group, while not holding their notes, did have access to them in the antenatal clinic. It is also possible that the fact of being in a study, and completing questionnaires, might have a 'Hawthorne' effect (Roethlisberger & Dickson 1939; Dahan *et al.* 1986, Oakley *et al.* 1986). This seems probable in the light of positive comments made by women when replying to an open-ended question 'How did you feel about being involved in the Newbury Maternity Care Study' (Elbourne 1987). Both the contamination and the 'Hawthorne' effect may have led to a dilution of the difference between the two policies

A woman's case records are not the most salient aspect of her care. When asked specifically about their preferences for the future, however, women clearly favoured case notes. This is in spite of a tendency for women to express preferences for forms of care which they have experienced personally, rather than an alternative which has merely been described to them (Porter & MacIntyre 1984).

Staff were also asked for their opinions about the two systems. Unlike the views of the women who were randomly allocated to one or the other of the two options, the staff experienced both policies, either before and after the experimental system was introduced, and/or while they were running concurrently. Opinions varied less by profession (midwifery, medical or clerical) or grade of staff, than by their geographical base. In general, Newbury-based staff stated a clear preference for the experimental system, whereas Reading-based staff expressed more mixed views. This might reflect real differences

Table 1. Comparison of the effects of the two randomly allocated policies: women's feelings

	Allocation			
	Case notes	Co-operation cards	Rate ratio	95% Confidence interval
Felt in control during antenatal care				
Newbury	66/132	41/119	1·45*	1·08–1·95
St Thomas'	21/97	11/102	2·01*	1·04–3·87
Both			1·56**	1·19–2·05
Felt could talk more easily with doctors and midwives				
Newbury	48/132	25/119	1·73**	1·16–2·59
St Thomas'	9/97	9/102	1·05	0·43–2·54
Both			1·56*	1·08–2·25
Would prefer to hold the same kind of record as held in index pregnancy in any subsequent pregnancy				
Newbury	112/123	62/106	1·56**	1·34–1·81
St Thomas'	83/93	39/101	2·31**	1·84–2·90
Both			1·83**	1·61–2·08

* *P*<0·05.
** *P*<0·01.

in the balance of advantages and disadvantages in the two places. The staff views are reported by Lovell & Elbourne (1987).

The results of this study have to be seen within the context of the wider society in which the concepts of privacy, confidentiality, secrecy and freedom of information have become topical. The Data Protection Act (1984) provides people with a general right of access to data held about them in a computerized form. Discussions about the specific case of patients' access to their medical records (manual or computerized) are currently taking place (NHS/DHSS 1984; DHSS 1985). Recently, the British Medical Association's conference of local medical committees voted that there should be no right of access by patients to their personal health data (British Medical Journal 1986). A decision from the Department of Health and Social Security is expected in 1987.

In the Newbury Maternity Care Study, women both had access to and held their notes There were almost no problems about women having access to their notes. Most difficulties thrown up by the system related to the women holding the notes, although any savings in clerical time arise from this aspect. Reports of the Steering Group on Health Services Information (NHS/DHSS 1981, 1985) have recommended that new systems for maternity data should be instituted for efficient audit of the services. These would require additional clerical resources. It has been estimated for example, that within the Oxford Region this would require one extra clerk per district (M. Goldacre, personal communication). In the light of current cash restraints, a policy of women holding their own records may be one way of saving clerical time without loss of administrative efficiency. If the observed time taken to retrieve and file notes found in our study is extrapolated nationally, an annual total of between 125 and 250 thousand hours of clerical time would be available for redeployment if policies of women-held case notes were introduced throughout the United Kingdom.

This entire debate may be overtaken by events—particularly the introduction of new forms of information technology. A computerized, multi-terminal records system might deal with many of the practical problems raised above (Cowie 1985), although it might create others, such as the imposition of a short-term financial burden on health districts already under severe cash restraints. It might also involve a dual system of manual records held by the women, with a computer file held in the relevant institution.

The only other randomized controlled trial in this field (Lovell *et al.* 1986) was conducted not in rural Berkshire but in inner London. The two studies found substantially the same positive results (Table 1) of the experimental policy (which in their case involved women holding their notes in pregnancy but not postnatally). As in Newbury, women were no more likely to forget to bring the bulky A4 set of case notes to their antenatal clinics or when they came into hospital in labour than they were the much smaller co-operation card. Nor were they any more likely to find the notes a nuisance to carry around. In addition, the St Thomas' study demonstrated that whereas no woman in the experimental group lost her records, more than a quarter of the control group reported that their hospital-held notes had been lost or temporarily mislaid at least once during their maternity care. This has important implications for the rare but very serious problems that might arise if a woman was admitted in an emergency when there was an urgent need to know her blood group, drug sensitivity, etc.

Clearly, a policy of women holding their case records cannot be presented as a panacea for all the ills of the maternity services. Nevertheless, there is consistent evidence from the only two randomized trials which have assessed this policy, that such a policy can have important beneficial effects both by enhancing women's feelings of control and their ease of communication with staff, and also by promoting a more efficient use of health service resources. In the light of these findings, serious consideration should be given to implementing this policy more widely.

Acknowledgments

We are grateful to all the women who gave up their time to complete the questionnaires, and to all the staff who discussed their views with us. We would also like to thank Trisha Simpson for clerical help at the recruitment stage; Alan Lodwick, Paul Griffiths and Hazel Ashurst for computing, Nicholas Wald, Robert Barlow and colleagues at the Department of Environmental and Preventive Medicine at St Bartholomew's Hospital for the urinary cotinine assays and advice on their interpretation; typing by Lesley Mierh, Jini Hetherington and Myrna Holmes; constructive criticism and support from many people, especially Alice Lovell, Hilary Thomas and Ann Oakley, and colleagues within the National Perinatal Epidemiology Unit. The Nuffield Provincial Hospitals Trust provided the funding for this project. Iain Chalmers is supported by the Department of Health and Social Security.

(For fuller details of this study, please write to Diana Elbourne.)

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Received 1 August 1986
Accepted 4 December 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp 620–635

Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy

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Summary. This paper reports the preliminary results of a cohort study of 4544 British women receiving hormone replacement therapy (HRT). These women were recruited at 21 specialist menopause clinics around Britain. Up to the end of June 1983, the mean duration of HRT use per woman was 67 months of which, on average, 43% was 'opposed' use. In general, however, both the amount of progestogen given and the number of days per cycle for which it was given was less than would have been the case if the women had been receiving modern opposed therapy. The major focus of the study was to monitor mortality and cancer incidence in the cohort. The mortality results were broadly reassuring: overall mortality was significantly lower than expected on the basis of national rates (relative risk 0·58) and mortality ratios were below unity for all specific causes of death examined apart from cancer of the ovary (relative risk 1·43, 95% confidence limits 0·62–2·82) and suicide or suspected suicide (relative risk 2·53, 95% confidence limits 1·26–4·54). The most likely explanation for the latter finding is selection bias—thus at least 7 of the 11 women who died from suicide or suspected suicide had a psychiatric history before receiving HRT The cancer incidence results were less reassuring, although they should be interpreted with some caution because cancer registry rates were used for comparative purposes. With this proviso, endometrial cancer risk was significantly elevated (relative risk 2·84, 95% confidence limits 1·46–4·96); many of the women concerned had taken therapy which was predominantly or entirely opposed although only one woman had received an opposed regimen which would now be considered adequately protective to the endometrium. Breast cancer incidence was also significantly increased (relative risk 1·59, 95% confidence limits 1·18–2·10); detailed analysis suggested that the use of unopposed ethinyl-oestradiol in particular might have undesirable effects on the breast.

In 1977, results were available from a number of controlled trials which suggested that short-term administration of hormone replacement therapy (HRT) was effective in alleviating the vasomotor symptoms of the menopause (Coope *et al.* 1975, Campbell & Whitehead 1977). In addition, there was evidence that longer term treatment could prevent postmenopausal osteoporosis and its complications (Horsman *et al.* 1977) and a widely held belief that such therapy could contribute to the general well-being of the women receiving it (Schleyer-Saunders 1960). On the negative side, the results of several case-control studies conducted in North America had indicated a 4–8 fold increase in the risk of endometrial cancer in women receiving conjugated equine oestrogens in the form of Premarin (Ayerst) (Smith *et al.* 1975; Ziel & Finkle

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1975; Mack *et al.* 1976). Little reliable information had been published at that time about the effects, if any, of HRT on breast cancer, ovarian cancer and cardiovascular disease (see Vessey & Bungay 1982).

It was against this background that the Medical Research Council (MRC) Working Group on Hormone Replacement Therapy decided to support our proposal that a cohort study should be done of women attending specialist menopause clinics in the United Kingdom. It was hoped we would generate new information about any relation between HRT and conditions such as breast cancer and fatal cardiovascular disease and that, in addition, it would be possible to determine whether or not the North American data about endometrial cancer applied to this country—it had, for example, been suggested that the dosages of oestrogen used here were generally lower than those used on the other side of the Atlantic.

In this paper, we describe the methods used in our study and summarize the main results to have emerged so far.

Subjects and methods

Recruitment to the study started on a prospective basis in 1978 after the co-operation of the staff at 21 menopause clinics had been obtained. To be eligible for recruitment, a woman had to be a current user of HRT attending one of the participating clinics and, in addition, had to have had at least 1 year's continuous treatment. This 'one year rule' was stipulated to exclude those women discontinuing therapy quickly as the study was concerned with the effects of longer term use of HRT. At the recruitment interview, each woman was asked about her obstetrical, gynaecological and past medical history. In addition, information was recorded about some social and physical characteristics (including height, weight, blood pressure, marital status, occupation and smoking history). A detailed HRT history was also documented up to the date of interview.

Recruitment to the study was slower than anticipated because a dramatic fall in HRT prescribing occurred between 1977 and 1980 (see Hunt 1985). It was therefore decided that recruitment should be enhanced retrospectively. Six clinics were judged to be suitable for retrospective recruitment in that all had treated a large number of women, some over a considerable period of time, and that all had comprehensive records which were readily accessible for review and had been kept for all women who had ever attended the clinic. The records in these six clinics were examined by the study co-ordinator and information was extracted to complete the recruitment form for those who fulfilled the study entry criteria. The date of recruitment was taken as the first clinic visit at which the woman concerned would have been eligible had the study been in progress at that time. This procedure led to reclassification of the date of entry to the study of some women who had been recruited prospectively in these six clinics.

All the recruitment forms were checked and coded and the data were entered on to the University ICL 2988 computer at Oxford. In addition, study participants were 'flagged' in the National Health Service Central Registries (NHSCR) in Southport and Edinburgh thus initiating a system of automatic notification of deaths and cancer registrations within the cohort.

A postal questionnaire was sent out in 1983 to 4387 of the 4544 women recruited to the study before the end of 1982. The response rate was almost 80%. The main purpose of the questionnaire was to elicit information on HRT use since entry to the study and to enquire about major morbidity. In addition, it was used to complete missing baseline data. Finally, it provided an opportunity to explore the broader social context of HRT use, but this aspect of our survey is not considered here.

From the above, it will be apparent that several means of identifying cancers occurring among the women in the study are available to us: (i) from the NHSCRs, (ii) from hospital and clinic notes where there has been occasion to review them, (iii) from notifications provided directly by doctors working in some clinics, and (iv) from self-reported information on the postal questionnaires.

Each notification of a death or of a cancer (regardless of the source of notification) has been followed up through the relevant doctor to confirm the diagnosis and to complete treatment details. In addition, a more detailed follow-up has been undertaken for cancers of the breast, endometrium and ovary. Thus an attempt was made to stage the breast cancers at the time of diagnosis from clinical notes using the TNM system (International Union against Cancer 1968) while for each diagnosis of endometrial or ovarian cancer, a request was sent to the histopathologist for the slides. These were then reviewed by an independent pathologist (Dr Clive Wells) at Oxford.

Subjects

The present analysis is limited to the 4544 women entering the study before the end of 1982. Of these, 7% were recruited before 1974, 29% between 1974 and 1977, 53% between 1978 and 1981, and 11% in 1982. Roughly equal proportions were recruited retrospectively and prospectively. Nearly 90% of the women came from only 10 of the 21 participating clinics. On a regional basis, 59% attended clinics in the London area, 12% Scottish clinics, 14% clinics in the North of England and 15% clinics elsewhere. Most of the women were aged 45–54 years at recruitment (60%) and at first use of HRT (63%). About 6% had never been married and nearly 20% had never given birth. Distributions by parity and by age at first term-birth were, so far as we could ascertain, broadly similar to those in the population at large (see Hunt 1985 for details). Women in the cohort tended, however, to be of higher social class than women in general (46% in social classes I or II; corresponding figure for 1971 census, 23%). With regard to smoking patterns, the women were unremarkable; 43% had never smoked, 16% were ex-smokers, 31% were current smokers and no information was available for the remaining 10%

Menopausal status at first use of HRT is shown in Table 1. Almost 36% of the women had already undergone hysterectomy at that time, some 2–2·5 times the proportion in the British population (see Hunt 1985). This is not surprising since hysterectomy (particularly when combined with bilateral oophorectomy) is often seen as an indication for HRT. Of the women with intact uteri, roughly equal numbers were either naturally postmenopausal or were pre- or perimenopausal at their first use of HRT. It should be noted that it may prove difficult or impossible to determine age at menopause in women commencing HRT before cessation of menses.

Table 1. Menopausal status at first use of hormone replacement therapy

Menopausal status	No. of women (%)
Hysterectomy	
with bilateral oophorectomy	859 (18·9)
at least one ovary intact	765 (16·8)
Natural menopause	1318 (29·0)
Radiation menopause	9 (0·2)
Irregular menses	1085 (23 9)
Regular menses	356 (7·8)
Status uncertain	152 (3 4)
	4544 (100·0)

Past oral contraceptive use was infrequent among the women in the cohort; at entry, 66% reported no use, 24% some use whereas for 10% no data were available. Amongst those reporting past use, about one-third had accumulated ≥5 years exposure.

Complete HRT histories up to the closure date for the present analysis (June 1983) are available for only 70% of the women in the cohort Details of treatment up to recruitment are, of course, known for all 4544 women, but are of very limited value. Accordingly, Table 2 provides data on total duration of use for the 3198 women for whom complete histories are available. It can be seen that 51% had taken HRT for more than 5 years and that the average duration of use per women was 67 months As expected, hysterectomized women had used HRT for somewhat longer periods than women with intact uteri (see Table 4, final column).

One striking feature of our study is the great variety of HRT preparations (and combinations of preparations) which have been used by the participants; indeed, over 175 different treatments are included in the survey coding schedule. Table 3 provides data on the 10 most commonly used regimens, but these considered together constitute only 71% of all use. Premarin taken alone accounted for only 17% of all HRT use, a finding in marked contrast to the figures in North American studies in which Premarin (Ayerst) used alone accounts for at least 80% of all use (see Hunt 1985). Furthermore, the treatment histories of many women in our study are characterized by several changes of preparation.

One important way in which HRT regimens can be grouped is according to whether or not oestrogen is opposed by a progestogen. Table 4 provides some data on this point, classified according to the uterine and ovarian status of the woman concerned at entry to the study. Women with intact uteri had received, on average, 21·3 months of unopposed use and 39·2 months of opposed use. By contrast, women who had

Table 2. Total duration of hormone replacement therapy (up to June 1983) for 3198 women with complete histories

Duration of use (months)	Women No	(%)	Months of use No.	(%)
12	35	(1·1)	409	(0·2)
13–24	302	(9·4)	5734	(2·7)
25–36	444	(13·9)	13 665	(6·4)
37–48	402	(12·6)	17 089	(8·0)
49–60	376	(11·8)	20 594	(9·6)
61–72	409	(12·8)	27 160	(12·7)
73–84	337	(10·5)	26 335	(12·3)
85–96	317	(9·9)	28 670	(13·4)
97+	576	(18·0)	74 306	(34·7)
Total	3198	(100·0)	213 962	(100·0)

Mean duration of use = 66·9 months.

already undergone hysterectomy and bilateral salpingo-oophorectomy at entry to the study had received, on average, 66·4 and 8·6 months of unopposed and opposed treatment respectively. Women who retained at least one ovary at hysterectomy were intermediate between the other two groups on these measures of HRT use.

We did not code the number of days for which progestogens were given in each cycle, nor the dose of the progestogens; indeed, these data were often unknown. It is, however, safe to say that most of the 'opposed' therapy received by women in our study was much less progestogenic than that which is generally given today.

Results

Mortality

In calculating the expected mortality experience of the cohort of 4544 women (from the time of recruitment to June 1983) use was made of the age specific death rates for England and Wales for the calendar periods 1966–70, 1971–75, 1976–80 and 1981–83. In computing woman-years at risk (see Coleman *et al.* 1986), survey participants left the analysis when they died, reached the age of 85, or (in some analyses) when the relevant organ was removed, but were not censored for any other reason.

Overall mortality ratios (together with 95% confidence limits) are shown in Table 5. Most of the ratios are low, varying between 0·34 and 0·69 (although some are based on very small numbers). The three ratios which fall outside this range merit specific comment. First, no deaths have occurred from endometrial cancer, despite an elevated incidence of this disease in the cohort (see below). Secondly, the slight excess of deaths from ovarian neoplasms is not statistically significant, but is a little worrying in view of the low mortality ratios seen for most other causes of death. The eight observed deaths from ovarian cancer are, however, based on the information recorded on the death certificate. A review of the relevant slides by our pathologist (Dr Clive Wells) led to the conclusion that two of these lesions had been misclassified, both, in his view, being secondary to primary colonic carcinoma. Finally, deaths due to injury, poisoning and violence are higher than expected and this excess is concentrated amongst suicide (6) and suspected suicide (5) giving a significantly elevated ratio for 'suicide' of 2·53. We considered that this excess of deaths from 'suicide' might reflect the fact that among those referred to menopause clinics are some who have severe and intractable psychological problems. This idea was supported by a review of the case records available to us; 7 of the 11 women who died had a history of psychiatric illness before HRT commenced and others, of course, may have done so. We were also concerned in case the progestogenic component of opposed HRT might have had a harmful psychological effect (see Hammarbäck *et al.* 1985). However, for the nine women who died and who had intact uteri,

Table 3. The 10 most commonly used hormone replacement preparations* in 3198 women

Preparation	Duration of use (months) Total (d)	Average per woman (d/3198)
1 Premarin	35 976	11·2
2 Premarin+norethisterone	23 167	7·2
3 Premarin+Neogest	20 406	6·4
4 Harmogen	12 854	4·0
5 Ethinyl-oestradiol	11 537	3·6
6 Progynova	10 952	3·4
7 Mestranol	10 901	3·4
8 Oestradiol and testosterone implant+norethisterone	9306	2·9
9 Cyclo-Progynova	8744	2·7
10 Oestradiol and testosterone implant	8077	2·5

* A key to trade names is provided in the Appendix.

Table 4. Total duration and average duration of hormone replacement therapy (unopposed, opposed and all) by uterine and ovarian status

Uterine and ovarian status at entry	Type and duration of use (months)					
	Unopposed use		Opposed use		All use*	
	Total	Average	Total	Average	Total	Average
Intact (n = 2046)	43 644	21·3	80 143	39·2	128 930	63·0
H−BSO† (n = 543)	28 558	52·6	6955	12·8	36 438	67·1
H+BSO‡ (n = 609)	40 453	66·4	5267	8·6	48 594	79·8
All women (n = 3198)	112 655	35·3	92 365	28·9	213 962	66·9

* 'All use' also includes use of progestogens and testosterone alone and periods of HRT use which were not clearly recorded as opposed or unopposed.

† H−BSO, Hysterectomy without bilateral salpingo-oophorectomy

‡ H+BSO, Hysterestomy with bilateral salpingo-oophorectomy.

the average duration of use of opposed HRT was 46·4 months and of unopposed HRT was 15·9 months, figures not much different from those for corresponding women in the cohort as a whole (39·2 months and 21·3 months respectively). The remaining two women had accumulated a total of 26 months opposed and 78 months unopposed treatment between them.

In view of the evidence that HRT might protect against certain types of cardiovascular disease, we also paid special attention to the low mortality ratios for ischaemic heart disease and cerebrovascular disease (see Table 5). The only interesting result to emerge was that the mortality ratios were lower at ages 45–64 (0·34 and 0·40 respectively) than at ages 65–84 (0·70 and 0·88 respectively). Once again, we wondered whether there was any evidence that opposed therapy might have a harmful (or, perhaps, a less favourable) effect on cardiovascular mortality,

Table 5. Mortality in the cohort by cause of death

Cause of death (ICD 9th revision)	Number of deaths			
	Observed (O)	Expected (E)	Ratio (O/E)	95% Confidence limits
Ca breast (174)	12	21·92	0·55	0·28–0·96
Ca endometrium (182; 179) (including uterus unspecified)	0	2·06 (1·39)*	—	0 –1·78
Ca cervix (180)	2	3·87 (2·82)*	0·52 (0·71)*	0·06–1·87 (0·08–2·56)
Ca ovary and uterine adnexa (183)	8	7·13 (5·59)*	1·12 (1·43)*	0·48–2·21 (0·62–2·82)
Other neoplasms	34	49·58	0·69	0·48–0·96
All neoplasms (140–239)	56	84·56	0·66	0·50–0·86
Ischaemic heart disease (410–414)	20	42·04	0·48	0·29–0·74
Cerebrovascular disease (430–438; 290·4)	14	21·64	0·65	0·35–1·09
Other circulatory disease	6	14·81	0·41	0·15–0·88
All circulatory disease	40	78·49	0·51	0·36–0·69
Suicide and suspected suicide	11	4·34	2·53	1·26–4·54
Other violent death	3	3·73	0·80	0·16–2·35
All deaths due to injury, poisoning and violence (800–998)	14	8·07	1·73	0·95–2·92
Other causes	14	41·38	0·34	0·19–0·57
All causes	124	212·50	0·58 (0·59)*	0·49–0·70

Ca, Carcinoma. *Adjusted figures for 'organs at risk' (i.e taking account of uterine and ovarian status where appropriate) especially from ischaemic heart disease. Eleven of the 20 women dying from ischaemic heart disease had intact uteri. Amongst these women, the mean duration of use of opposed HRT was 29·8 months and of unopposed HRT was 19·6 months (corresponding figures for cohort as a whole, 39·2 months and 21·3 months respectively). Among the remaining nine women who had had a hysterectomy, almost all the HRT use was unopposed (mean duration 47·1 months). These data do not suggest that opposed therapy is hazardous with regard to ischaemic heart disease but clearly much more information is needed before firm conclusions can be drawn.

Finally, it should be noted that we analysed the mortality data in our study (both overall and for individual causes) in many other ways taking into account age, calendar period, interval since first exposure to HRT and duration of HRT use at entry to the study. In addition, we adjusted the mortality ratios to take account, as far as was possible, of the influence of social class (see Hunt 1985). These analyses added little to what has already been described and, in the interests of space, the results are not given here.

Morbidity

Analyses of cancer incidence in the study have been confined so far to four sites (breast, endometrium, ovary, cervix). The expected figures presented here are based on rates from the Birmingham Cancer Registry. The calendar periods 1966–72, 1973–77 and 1978–82 were considered separately in the analysis and the closure date was set at December 1982, earlier than for the mortality analysis because of uncertainty about completeness of ascertainment of more recently diagnosed tumours. Women left the analysis on the date of diagnosis of their tumour, on the date of their death, on reaching the age of 85 or (in some analyses) when the relevant organ was removed, but were not otherwise censored.

Although complete treatment histories were obtained (so far as possible) for all women developing cancer, data about HRT use subsequent to recruitment to the study were not available for about 30% of the cohort as a whole. Accordingly, in view of their importance, endometrial cancer and breast cancer risks have been investigated by case-control methods as well as by the cohort approach.

Our overall findings on the incidence of cancer are summarized in Tables 6 and 7. Detailed reference is made to these tables in the paragraphs which follow.

Cancer of the endometrium

The incidence of endometrial cancer was significantly elevated among women in the cohort to almost three times the expected rate (adjusted ratio, 2·84, Table 6). There was also evidence of a rising trend in ratio with interval since first use (Table 7) although the trend does not reach statistical significance ($\chi^2_{(1)}$ trend = 1·27).

We undertook a detailed analysis of the HRT preparations taken by the 12 women with endometrial cancer together with two additional women who were diagnosed after December 1982. These women had taken a bewildering array of preparations, far too complex to reproduce in full here (see Hunt 1985). Summary information is, however, given in Fig. 1 from which it is apparent that 10 of the 14 women had taken HRT for more than 36 months before

Table 6. Incidence of cancer in the cohort

	Number of cases			
Site of cancer	Observed (O)	Expected (E)	Ratio (O/E)	95% Confidence limits
Uterine body (endometrium)	12	6·51 (4·23)*	1·84 (2·84)*	0·95–3·22 (1·46–4·96)*
Breast	50	31·38	1·59	1·18–2·10
Ovary	6†	6·92 (5·21)‡	0·87 (1·15)‡	0·32–1·89 (0·42–2·51)‡
Certvix uteri	2	6·75 (4·25)*	0·30 (0·47)*	0·03–1·07 (0·05–1·70)*

* For women with intact uteri

‡ Two cases included in the mortality analysis rejected from this analysis (both probably had their origin in the colon)

† For women with both ovaries intact.

Table 7. Cancer incidence by interval since use of hormone replacement therapy (HRT)

	Site of cancer											
	Endometrium*			Breast			Ovary†			Cervix*		
Interval since first use of HRT (years)	O	E	O/E (95% CI)	O	E	O/E (95% CI)	O	E	O/E (95% CI)	O	E	O/E (95% CI)
0–4	4	1·90	2·11 (0·57–5·39)	20	14·32	1·40 (0·85–2·16)	1	2·44	0·41 (0·01–2·27)	2	2·13	0·94 (0·11–3·39)
5–9	6	1·98	3·03 (1·11–6·60)	20	13·80	1·45 (0·88–2·24)	4	2·35	1·70 (0·46–4·36)	0	1·86	— (0–1·97)
10+	2	0·35	5·71 (0·64–20·63)	10	3·26	3·07 (1·47–5·64)	1	0·42	2·38 (0·03–13·25)	0	0·26	— (0–14·11)
Total	12	4·23	2·84	50	31·38	1·59	6	5·21	1·15	2	4·25	0·47

* Expected rates based on organs at risk.

O, Observed number of cases; E, expected number of cases; CI, confidence limits.

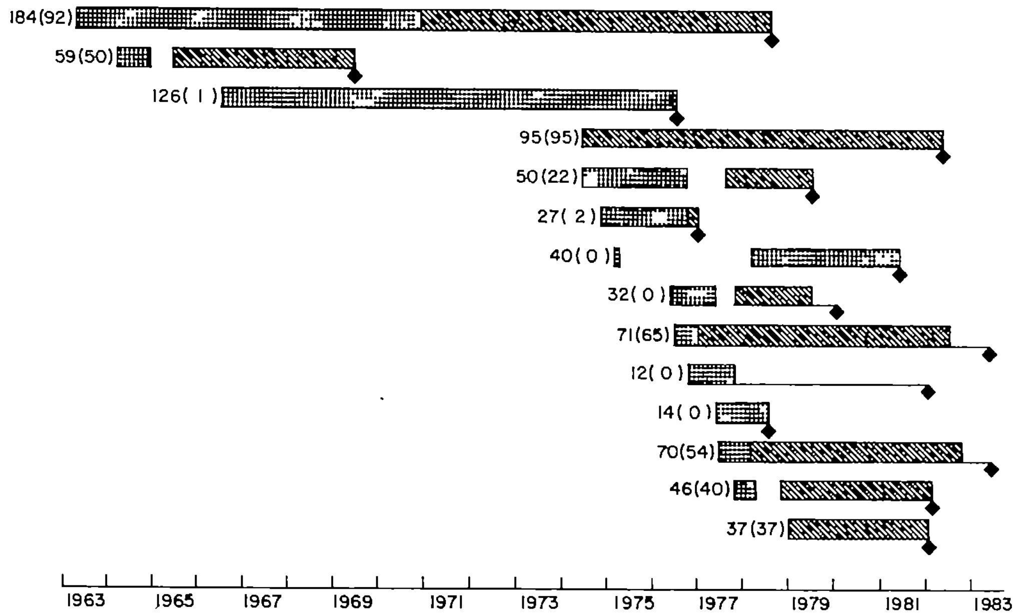

Fig. 1. Duration of opposed (▩) and unopposed (▤) treatment preceding diagnosis of endometrial cancer in 14 women. ◆, Date of diagnosis; 46, total number of months of treatment; (40), number of months of opposed treatment.

developing endometrial cancer (mean duration of use, 61 months). More important, 8 of the 14 women had taken therapy which was predominantly or entirely opposed, an unexpected and worrying finding. Accordingly, we arranged for each of the individual treatment histories to be examined by a gynaecologist who has worked extensively in this field (Mr Malcolm Whitehead) who concluded that only one woman had received an opposed regimen which would now be considered sufficiently protective to the endometrium on the basis of recent clinical work (Whitehead *et al.* 1982). The remaining women had been given progestogens for too few days in each month and/or had been prescribed progestogens (notably 1 mg megestrol acetate or 1 Neogest (Schering) tablet) which are now thought to be ineffective in protecting the endometrium even if they are taken for 12 days in each month.

On pathological review (by Dr Clive Wells), all 14 endometrial cancers were adenocarcinomas. Nine tumours were successfully staged; 8 were stage I, the ninth being stage III. Grading was possible for 12 of the tumours; 8 were grade 1 (well-differentiated), 3 were grade 2 (moderately differentiated) and only 1 was grade 3 (poorly differentiated). It may be noted that one further case which was reported to us as endometrial cancer was rejected from our analysis as Dr Wells considered the lesion not to be malignant.

We also conducted a case-control analysis in which each woman with endometrial cancer was matched with three other women in the cohort who were randomly selected from all those who (i) were born in the same year as the case, (ii) had no history of endometrial cancer, (iii) were still alive and in the study on the date of diagnosis of the case, and (iv) had an intact uterus. Obviously, the controls had to have had at least 1 year's use of HRT, so that there was no unexposed referent group. Every effort was made to obtain a complete treatment history for all the controls by contacting the doctors who had cared for them. The results of this case-control analysis are not reproduced here; they did not, however, show any clear differences between the groups either in terms of duration of HRT use (although this was somewhat longer among the cases) or in terms of opposed compared with unopposed treatment.

Cancer of the breast

The incidence of breast cancer in the cohort was also found to be significantly elevated (ratio

1·59, Table 6). As with endometrial cancer, Table 7 shows that there was evidence of a positive trend in ratio with interval since first use of HRT ($\chi^2_{(1)}$ trend = 2·97, P = 0·08).

Adjustment of the ratios (so far as possible) for social class had little effect and the increased incidence also persisted when national rates were used (see Hunt 1985). There is, however, some evidence that diagnosis might have been accelerated among the women using HRT, perhaps as a result of increased surveillance. Thus of the 40 breast cancers we were able to stage, 27 (68%) were in clinical stage I at diagnosis, a much higher proportion than that reported by Sicher & Waterhouse (1973)–37·9%, or by De Bono & Kingsley Pillers (1978)–33·3%, but not much different from that reported by Greenberg *et al.* (1985)–61·7%. It should be noted that 15 of the 27 stage I cancers were T_2, that all 50 cancers were invasive, that there was no difference in the proportion of stage I cancers when current users of HRT were compared with ex-users, and that few, if any, women with breast cancer had been diagnosed as a consequence of screening by mammography.

When breast cancer incidence was analysed by uterine and ovarian status at entry to the study, the risk ratio was highest in women who had had a prior hysterectomy with conservation of at least one ovary and lowest in women with intact uteri (Table 8). This result was unexpected and is difficult to interpret since early bilateral oophorectomy (but not hysterectomy) has been shown in many studies to confer protection against breast cancer.

To explore this observation further, and to enable us to try to obtain some information about any relation between duration and type of HRT use and risk of breast cancer, we undertook a case-control analysis along the same lines as that already described in relation to endometrial cancer. On this occasion we did not, of course, require the controls to have an intact uterus. In addition, we reduced the number of controls per case to two and included four additional breast cancer cases diagnosed after December 1982.

When comparisons were made between the two groups of women, it was found that the cases tended to be of lower parity and to be slightly older when they first gave birth than the controls, although neither of these differences was statistically significant. These observations are, of course, consistent with the known epidemiology of breast cancer. Cases were more likely to have had a prior hysterectomy than the controls (P<0·01), reflecting the higher risk ratio seen in hysterectomized women in the cohort analysis (Table 8).

Comparisons of duration of use, both overall and of opposed and unopposed HRT, are shown in Table 9 for the 53 cases and 97 controls for whom complete data were available. There is some evidence that cases had longer overall durations of treatment than controls, although the relation is not entirely straightforward; the $\chi^2_{(1)}$ value for trend just falls short of significance at the 5% level. The most marked differences are seen in the tails of the distribution: only 2 cases as compared with 23 controls had <2 years' use, whereas 10 cases as compared with only 9 controls had used therapy for >8 years. The distributions showing use of opposed and unopposed HRT separately do not contribute much, although the value of $\chi^2_{(1)}$ for trend again borders on statistical significance for unopposed treatment.

A multivariate analysis (logistic regression for matched sets) was undertaken in an attempt to disentangle the effects of duration of use and of ovarian and uterine status; thus we were aware that women who had undergone hysterectomy tended to have taken HRT for longer than other women and to have taken more unopposed

Table 8. Breast cancer incidence by uterine and ovarian status (at entry)

	Number of cases			
Ovarian/uterine status at entry	Observed (O)	Expected (E)	Ratio (O/E)	95% (CI)
Uterus intact	24	20·18	1·19	(0·76–1·77)
Hysterectomy with bilateral oophorectomy (H+BSO)	10	6·01	1·66	(0·80–3·06)
Hysterectomy (at least one ovary intact) (H−BSO)	16	5·19	3·08	(1·76–5·01)
Total	50	31·38	1·59	(1·18–2·10)

Table 9. Comparisons of use of hormone replacement therapy (HRT) between breast cancer and controls

	Overall duration of treatment (months)					
	12–24	25–48	49–72	73–96	97+	Total
Cases	2	23	16	2	10	53
Controls	23	33	18	14	9	97
Total	25	56	34	16	19	150

$\chi^2_{(1)}$ for trend = 3·38 (NS)

	Duration of unopposed treatment (months)						
	0	1–24	25–48	49–72	73–96	97+	Total
Cases	8	16	11	11	2	5	53
Controls	19	39	21	9	5	4	97
Total	27	55	32	20	7	9	150

$\chi^2_{(1)}$ for trend = 3·52 (NS)

	Duration of opposed treatment (months)						
	0	1–24	25–48	49–72	73–96	97+	Total
Cases	24	12	8	4	3	2	53
Controls	43	21	19	8	4	2	97
Total	67	33	27	12	7	4	150

$\chi^2_{(1)}$ for trend = 0·04 (NS)

therapy (Table 4). In this analysis, duration of treatment was divided into four groups (12–30, 31–48, 49–72, 73+ months); these groupings were chosen by dividing the number of subjects under study as nearly as possible into quartiles. The analysis was conducted on 48 matched sets.

A number of different models were fitted to the data, all of which gave broadly comparable results. Table 10 may be taken as representative. Increased relative risks of breast cancer are apparent for women with hysterectomy, with or without bilateral salpingo-oophorectomy, in comparison with women with intact uteri. Likewise, increased relative risks of breast cancer are apparent for women taking HRT for durations longer than 30 months in comparison with those with shorter durations of use. The substantial magnitude of the relative risks associated with prolonged HRT use is, of course, a reflection of the small number of cases of breast cancer with short durations of use (Table 9). As expected, the adjusted relative risks are generally appreciably smaller than the crude relative risks. Nonetheless, all the relative risks remain substantially in excess of unity indicating that the effect of duration of HRT use is only partially explained by the effect of type of menopause and vice versa.

Duration of use of unopposed and opposed HRT were also fitted into various models, both singly and together. These analyses were no more illuminating than that shown in Table 10 and no obvious patterns emerged.

One further way in which use of HRT was considered in the case-control analysis was to compare the average duration of use of particular preparations (and combinations) (Table 11). It is unwise to draw firm conclusions from such an analysis, especially on the basis of small numbers of subjects, but ethinyl-oestradiol was much more extensively taken by the cases than by the controls. Use of this steroid was, of course, largely concentrated among hysterectomized women and particularly among those who retained their ovaries. Only three cases are known to have taken daily doses of ethinyl-oestradiol in excess of 50 µg.

Cancer of the ovary

The incidence data for ovarian cancer are unremarkable (Tables 6 and 7). Histological review of the slides, however, proved interesting. Apart from the two tumours excluded from the morbidity analysis because Dr Wells considered them to be secondary to colonic cancer, there was one mixed mesodermal tumour while two tumours were endometrioid in type. One woman developed ovarian cancer 6 years after a documented hysterectomy and bilateral salpingo-oophorectomy, presumably from residual ovarian tissue.

Cancer of the cervix

Only two cases of invasive cervical cancer were observed among women in the cohort (adjusted ratio 0·47, see Tables 6 and 7). This finding may reflect more careful screening of HRT users for

Table 10. Risk of breast cancer by uterine and ovarian status and by duration of hormone replacement therapy (HRT) (95% confidence limits in parentheses)

Variable	Relative risk (unadjusted)	Relative risk (adjusted)
No hysterectomy	1·0	1.0
Hysterectomy without BSO	3·4 (1·4– 8·4)	2·9 (1·1– 7·5)
Hysterectomy with BSO at age (years)		
≤39	7·1 (0·6–89·8)	2·2 (0·1–34·3)
40–44	2·4 (0·5–11·1)	1·9 (0·4– 9·1)
45–49	2·0 (0·2–17·5)	1·3 (0·1–12·9)
≥50	2·3 (0·5–10·7)	2·7 (0·5–15·1)
HRT use (months)		
12–30	1·0	1·0
31–48	5·2 (1·8–15·6)	4·8 (1·5–15·6)
49–72	6·1 (1·8–20·4)	5·3 (1·4–20·2)
≥73	4·8 (1·3–17·0)	3·6 (0·9–15·0)

BSO, Bilateral salpingo-oophorectomy.

Note. The substantial magnitude of the relative risks associated with prolonged HRT use is a reflection of the small number of cases of breast cancer with short durations of use (see Table 9).

Table 11. Use of 10 most commonly taken preparations by women with breast cancer and matched controls

	Women with breast cancer (*n* = 53)				Matched controls (*n* = 97)			
		Duration of use (months)				Duration of use (months)		
Preparation	No. of users	Total	Average	Average per user	No. of users	Total	Average	Average per user
1 Premarin	24	777	14·7	32·4	37	834	8·6	22·5
2 Premarin+ norethisterone	6	223	4·2	37·2	19	634	6·5	33·4
3 Premarin+Neogest	13	319	6·0	24·5	15	265	2·7	17·7
4 Harmogen	13	286	5·4	22·0	23	336	3·5	14·6
5 Ethinyl-oestradiol	18	705	13·3	39·2	12	141	1·5	11·8
6 Progynova	8	151	2·8	18·9	20	234	2·4	11·7
7 Mestranol	2	170	3·2	85·0	2	217	2·2	108·5
8 Oestradiol and testosterone implant+ norethisterone	1	23	0·4	23·0	6	174	1·8	29·0
9 Cyclo-Progynova	9	60	1·1	6·7	8	112	1·2	14·0
10 Oestradiol and testosterone implant	0	0	—	—	6	178	1·8	29·7

uterine disease; most cervical lesions are likely to have been detected and treated at an early (pre-invasive) stage.

Discussion

HRT has been taken by large numbers of women in the United States, often for prolonged periods of time. Furthermore, until recently, most women in the United States who were prescribed HRT received Premarin. These circumstances have made it easy for American epidemiologists to study the long-term effects of HRT using the case-control approach and this is reflected in the published literature (Vessey 1985).

The position is entirely different in the United Kingdom where the level of use of HRT has remained low and where long-term use is very uncommon. Furthermore, a wide variety of

HRT preparations have been used in Britain. Accordingly, case-control studies are generally impracticable and the cohort approach seems more promising. The MRC Working Group on HRT conducted a feasibility study in 1977 for a cohort study based in general practice, but the low levels of prolonged HRT use that were found led to this approach being abandoned. Accordingly, the design used in the present study was adopted. The investigation has a number of obvious inadequacies including its relatively small size, the selected nature of the population studied, the absence of an internal control group (attempts to recruit such a group were made, but failed) and the incompleteness of some of the information gathered. Nonetheless, we believe that some important findings have emerged.

The most striking feature of our analysis of mortality is the generally low level of the mortality ratios (with the notable exception of the data relating to 'suicide'). How should this observation be interpreted? Few other investigations have considered the effect of HRT on general mortality. Bush *et al.* (1983), however, studied 2269 white women, aged 40–69 years, who had been followed up for an average of 5·6 years in the Lipid Research Clinics Program Study. They reported that the relative risk of death in users of HRT (predominantly Premarin) was only 0·37 in comparison with non-users but their study has major limitations including lack of information on dosage and duration of HRT use and on cause specific mortality. Two further recent studies have also considered overall mortality among HRT users. Wilson *et al.* (1985) found no difference in all cause mortality (or mortality from cardiovascular disease) between oestrogen users and non-users despite the fact that the women taking oestrogens had better coronary disease risk profiles well in advance of starting therapy. Stampfer *et al.* (1985), basing their analysis on 379 deaths, present an age-adjusted relative risk for total mortality of 0·5 when comparing ever users of oestrogens with never users and of 0·3 when comparing current users with never users. However, after exclusion of women with diagnosed cancer (or with coronary heart disease) at baseline, age-adjusted relative risks for total mortality became 0·9 for ever use of oestrogens and 0·7 for current use.

Other studies have considered the effect of HRT on mortality from particular diseases, notably endometrial cancer and cardiovascular disease. Unopposed oestrogens can undoubtedly cause an excess of incident endometrial cancers (see Vessey 1985) but the tumours tend to be of favourable grade and early stage, and there is no obvious adverse effect of treatment on mortality from this disease (Vessey & Lawless 1984). Several investigators have provided evidence to suggest that unopposed oestrogens used by postmenopausal women may confer protection against mortality (and morbidity) from coronary heart disease (see Bush & Barrett-Connor 1985; Vessey & Hunt 1987). The significant deficit of deaths from ischaemic heart disease (mortality ratio 0·48) seen in our study is consistent with this interpretation. There is, of course, concern that the addition of a progestogen to the oestrogen component of HRT might be damaging to the cardiovascular system (see Vessey & Hunt 1987). In this context, however, it should be remembered that although 43% of the HRT taken by women in our cohort was opposed (Table 4), the doses of progestogen involved were generally low and administration was typically for only a few days in each cycle. Certainly, there was no suggestion in our study that women dying from ischaemic heart disease were more likely to have used protestogen-containing preparations than other women.

Many research workers have been concerned about the extent to which the selected nature of the populations they have studied may account for the low mortality ratios (and low cardiovascular morbidity) they have found (Bush *et al.* 1983; Wilson *et al.* 1985; Stampfer *et al.* 1985) and this is a problem in the interpretation of our results. We know that our cohort (consisting of long-term users of HRT who attended menopause clinics) is, by definition, atypical given the inequality of access to menopause clinics (and other sources of HRT) both regionally and by various social criteria and the generally low levels of prescribing in this country. Certainly, the high social class distribution of the cohort could, quite plausibly, be interpreted as a manifestation of selection. Accordingly, standardization by social class was (as far as possible) carried out, but this made very little difference to the mortality ratios.

It is, of course, to some extent inevitable that 'high risk' women (i.e. those deemed to have contraindications to therapy) will be less likely than others to be prescribed HRT. This 'healthy volunteer' effect would be expected to be maximal at the beginning of the study and to decline with time. In our study, there is, in fact, no striking trend towards increasing mortality ratios with increasing interval since starting to use HRT, although given the relative youth of the population and the relatively short average duration of follow-up (5·9 years) it is, perhaps, too early to see such an effect. Nonetheless, the overall mortality ratio in the shortest risk interval (0–4 years since first exposure) was slightly lower (0·49) than in other intervals, and examination of cause-specific mortality ratios showed that the three causes of death with the lowest mortality ratios in the shortest risk interval were cancers of the breast and ovary and ischaemic heart disease. This, perhaps, provides evidence that some women were initially selected out of the study on the basis of ill health, but the numbers are too small to be sure.

Another possible explanation for the deficit of mortality is, of course, incomplete reporting of deaths. There is, however, no indication that this explanation has any validity: checks, such as on the completeness of 'labelling', suggest that the reliability of death notification from the NHSCRs is high.

The excess of deaths from 'suicide' warrants special comment. We have shown that 7 of the 11 women who died had a history of psychiatric illness before starting to use HRT and that there was no obvious tendency for these women to have used progestogen-containing preparations. In addition, most of the 11 deaths occurred in women aged 55–64 years who had first used HRT 5–9 years previously. Taking all these observations together it seems likely that the excess of deaths from 'suicide' is a manifestation of selection.

Our study, therefore, provides broadly reassuring evidence on the effects of HRT on mortality. It would be premature, however, to claim that HRT is protective since the low mortality ratios are projected across almost all the causes of death studied and the women in the cohort are a selected population. If the deficit of deaths had been concentrated within cardiovascular disease, the biological plausibility of the results would be more convincing.

Our data on the incidence of endometrial cancer are similar to those reported from the United States although the overall relative risk is lower than that found in most previous studies (see Vessey 1985). Furthermore, we failed to find any obvious relation between risk and duration of use. The most important feature which distinguishes our results from those previously published, however, is that they are derived from a population which has experienced substantial use of opposed HRT. We have shown quite clearly that endometrial cancer can occur in women using inadequately opposed therapy. In our view, it is most important that the poor performance of earlier opposed therapy is widely recognized. The use of progestogens in conjunction with oestrogens by peri- or postmenopausal women carries with it some minor side effects, and the possibility remains (although our data offer no support to the idea) that opposed therapy may eliminate any beneficial effect which oestrogens used alone may have on the risk of coronary heart disease. It is obviously undesirable for progestogens to be given in such a way as not even to confer the intended benefit of protecting against endometrial cancer.

Research on the relation between HRT use and breast cancer has given inconsistent results (see Vessey 1985). Of particular interest in the context of the present study is the work of Hoover *et al.* (1976) which concerned 1891 women in Louisville, USA, who had been given long-term treatment with Premarin and followed up for an average of 12 years. In total, 49 cases of breast cancer were observed while 39·1 would have been expected on the basis of rates in the general population. The relative risk increased with follow-up duration, progressing to 2·0 after 15 years. In addition, after 10 years of follow-up, two factors normally related to a low risk of breast cancer, multiparity and oophorectomy, no longer imparted a protective effect.

Most of the remaining studies are of the case-control type; some have suggested a small adverse effect of Premarin use on breast cancer risk, others have not (Kaufman *et al.* 1984; Vessey 1985; Brinton *et al.* 1986). Gambrell *et al.* (1983) have reported results from a cohort study conducted at Wilford Hall Medical Center, USA, which suggest that the addition of progestogen to oestrogen therapy decreases the risk of breast cancer in postmenopausal women. This study, however, suffers from a number of deficiencies including uncertainty about completeness of follow-up, non-comparability of the women in the different treatment groups and small size.

Our data on breast cancer, while far from conclusive, do provide some cause for concern.

First, we are worried about the high incidence of the disease in the face of low mortality. Our intepretation of the latter observation is that women with clinically recognizable breast cancer and perhaps those at high risk of the disease were selected out of the cohort as being unsuitable for HRT. In these circumstances, one might have expected to see a low incidence of breast cancer as well as a low mortality if HRT had no harmful effect, but this has not occurred. In due course, it seems likely that mortality from breast cancer in the cohort will rise. Secondly, we are concerned about the unexpected association between uterine and ovarian status and breast cancer risk. As in the study by Hoover *et al.* (1976) we suspect that this observation relates to the pattern and type of HRT use by women undergoing artificial menopause although we have failed to prove that this is so, perhaps on account of imperfections in our data on exposure, the great complexity of the inter-relationships, and the possibility that some treatments (for example, unopposed ethinyloestradiol) are associated with a risk while others are not. Again, although our findings on duration of use in relation to risk are not clear cut, there is a definite deficiency of very short-term use and a definite excess of very long-term use amongst the women with breast cancer (Table 9). Finally, our failure to find any obvious differences in risk associated with type of therapy (i.e. unopposed compared with opposed) may merely reflect the fact that very small amounts of progestogen were taken by most women.

There is, of course, the possibility that we may to some extent have overestimated the relative risk of breast cancer in the cohort analysis. First, we used cancer registry rates to calculate expected numbers; any incompleteness of cancer registration would inflate the relative risk. During the course of our study, we found some breast cancers which appeared not to have been registered (K. Hunt & M. Coleman, unpublished observations). However, we had chosen to use Birmingham cancer registry rates for comparative purposes because that registry is believed to achieve near completeness of registration (Waterhouse 1982); it is of interest that none of our apparently unregistered breast cancer cases came from the West Midlands. It should also be noted that the means we used to identify cancers occurring among women in the study cohort may have missed some cases, thus producing an error in the opposite direction. Secondly, diagnostic surveillance bias may have operated in our study, thus advancing the date of diagnosis of some breast cancers. This idea is supported by the finding that the distribution of stage was relatively favourable amongst the breast cancer cases. In our view, however, it is unlikely that the date of diagnosis would have been brought forward sufficiently to explain more than a small part of the excess incidence we have found. Further follow-up of the cohort should help to settle this question. The fact that the women in our cohort were of higher social class than the general population should also be borne in mind, although analyses taking this consideration into account (as far as was possible) altered our findings little.

In conclusion, this study has thus far shown no adverse association between HRT and mortality, with the exception of the excess death rate from 'suicide' which probably represents a selection effect. The data are compatible with a reduced risk of cardiovascular mortality in HRT users, but we cannot be sure that this is not also a selection effect. The incidence of endometrial cancer is increased about three-fold and there is no doubt that this disease can be a problem in women taking oestrogens inadequately opposed by progestogens. The findings in regard to breast cancer give some cause for concern, but cannot be regarded as conclusive.

We plan to continue the follow-up of women in our cohort in the hope of extending knowledge about the long-term effects of HRT. We believe, however, that in the final analysis it will be possible to assess the benefits and risks of HRT adequately only within the setting of a large-scale randomized controlled trial. We are hoping that research finance might be found for such an enterprise.

Acknowledgments

This study would not have been possible without the kind cooperation of those in the participating clinics. We would, therefore, like to express our thanks to: Dr A. Anderson (deceased), Mr K. J. Anderton, Dr M. Aylward, Mr R. Beard, Dr J. Coope, Dr J. Ginsburg, Mr B. Hackman, Dr V. Houghton, Dr M. Jones, Dr T. Lind, Dr J. Maddison (deceased), Dr H. McEwan, Mr J. McGlone, Mr D. McKay Hart, Mr J. McQueen, Mr G. A. Morewood, Dr C. Nordin, Mr A. D. Parsons, Dr M. Peacock, Mr M. Pugh, Mr P. Sanders, Mr J. Studd, Mrs T. R. Varma, Mr M. Whitehead, and all clinical and non-clinical colleagues who have been involved with the study. We would also like to thank Dr D. Yeates, Dr C. Wells, Mrs D. Collinge and Mrs J. Challenger and the staff in the Survey Section of the National Health Service Central Registries. The Medical Research Council kindly provided financial support.

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Received 15 August 1986
Accepted 12 December 1986

Appendix

Key to trade names

Premarin—conjugated equine oestrogens 0·625 mg, 1·25 mg or 2·5 mg (Ayerst).
Neogest—norgestrel 75 μg (Schering).
Harmogen—piperazine oestrone sulphate 1·5 mg (Abbott).
Progynova—oestradiol valerate 1 mg or 2 mg (Schering).
Cyclo-Progynova—oestradiol valerate 1 mg (11 tablets); oestradiol valerate 1 mg, levonorgestrel 0·25 mg (10 tablets) (Schering).

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 636–642

Screening for Down's syndrome using an iso-risk curve based on maternal age and serum alpha-fetoprotein level

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Summary. On the basis of the significantly different distributions of maternal serum alpha-fetoprotein (AFP) levels in 86 pregnancies associated with fetal Down's syndrome and in 2018 unaffected pregnancies, an iso-risk curve for Down's syndrome was constructed. An iso-risk curve shows, for women of all ages, which combinations of maternal age and level of maternal serum AFP result in the same risk of carrying a fetus with Down's syndrome. A 1:400 risk of Down's syndrome, corresponding to the risk of a 35-year-old woman, was chosen as the lowest risk indicating referral for amniocentesis. If all women, irrespective of their age, are offered amniocentesis, when their risk of carrying a Down's syndrome fetus is 1:400 or higher, 53% of the affected fetuses can be detected as compared with 28% of the affected fetuses diagnosed at present in women above 35 years of age.

Since Merkatz *et al.* (1984) observed that pregnancies associated with fetal Down's syndrome were associated with reduced levels of maternal serum alpha-fetoprotein (AFP), several studies have examined the possibility of using serum AFP as a screening test for Down's syndrome (Cuckle *et al.* 1984; Murday & Slack 1985; Fuhrmann *et al.* 1984; Cowchock & Ruch 1984). These studies have mainly concentrated on identifying a high-risk group of younger women, who are not offered amniocentesis at present. Since the inverse relation between maternal serum AFP and Down's syndrome also implies that women with high levels of maternal serum AFP have a relatively low risk of Down's syndrome (Editorial 1985), it may be possible to define a low-risk group as well as a high-risk group among women who are offered amniocentesis because they are over 35 years of age The present study attempts to assess the use of maternal serum AFP in combination with maternal age as

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a screening test for Down's syndrome in all pregnant women.

Subjects and methods

Unaffected pregnancies

Since 1 March 1980, a multicentre study of maternal serum AFP screening has been in progress in four centres in Denmark (Nørgaard-Pedersen *et al.* 1985). All samples for AFP determination were analysed in a single laboratory by polyethylene glycol radioimmunoassay, using a kit from Amersham (Nørgaard-Pedersen *et al.* 1985). Serum AFP results at 14–20 weeks gestation from 2018 unaffected singleton pregnancies were used to calculate reference intervals and determine the median for each gestational week. Maternal serum AFP was expressed in multiples of the median (MoM) for the appropriate gestational age. Gestational age in completed weeks at the time of maternal serum sampling was based on the interval since the last menstrual period.

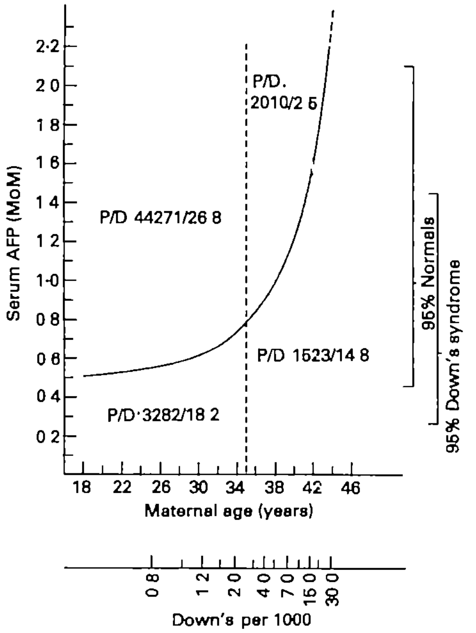

Fig. 1. Iso-risk curve (1:400) for Down's syndrome based on maternal age and serum AFP (expressed in MoM), 95% reference intervals for normals (n=2018) and Down's syndrome (*n*=86) are shown. The median serum AFP in Down's syndrome pregnancies was 0·64 MoM. The lowest abscissa (Down's per 1000) shows the risk of having a Down's syndrome infant based on age alone. P, number of pregnancies; D, number of Down's syndrome cases

Trisomy 21 pregnancies

Antenatally diagnosed cases. Between 1 January 1980 and 31 December 1985, the Danish cytogenetic central register recorded 157 cases of trisomy 21 diagnosed on amniotic fluid cell examination from the reports of the three cytogenetic laboratories doing prenatal diagnosis in Denmark. Eighty-eight (56%) women had not had a serum AFP determination. Four women were excluded, because the serum sample had been collected before 13 completed weeks gestation (3 cases) or because a congenital anomaly known to be associated with increased levels of maternal serum AFP was found concomitantly with Down's syndrome (1 case). The present study therefore included 65 women with a known level of maternal serum AFP in an antenatally diagnosed trisomy 21 pregnancy (The results for 25 of these women have been published previously by Tabor *et al.* (1984).)

Neonatally diagnosed cases. Between 1 January 1981 and 31 December 1985, 202 infants with Down's syndrome were reported to the Danish cytogenetic central register. Twenty-one (10%) of the mothers had a pregnancy serum AFP determination.

Thus, the present study included a total of 86 women with a known serum AFP level associated with Down's syndrome. The concentration of maternal serum AFP in these pregnancies was expressed as multiples of the median concentration of maternal serum AFP from unaffected pregnancies from the same gestational week. (The specific data are available from the authors upon request.)

Results

For the unaffected pregnancies, the logarithmic distribution of maternal serum AFP, expressed as MoM, was found to be well described by a normal distribution with a mean of 0 and a standard deviation of 0·168. There was no correlation between values of serum AFP and maternal age. The 95% confidence interval of the maternal serum AFP values, expressed as MoM, is shown in Fig 1. The median was 1·0 MoM.

In the 86 pregnancies associated with Down's syndrome the mean of log MoM was −0·197 (SD

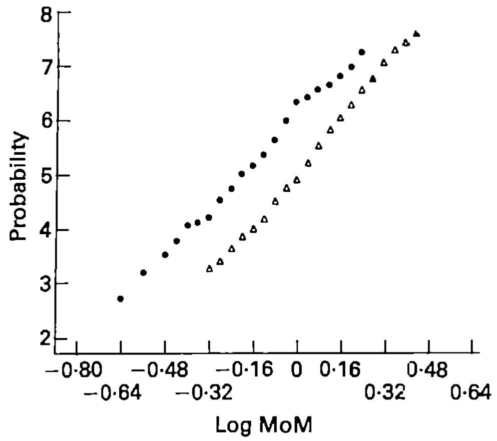

Fig. 2. Probability plot showing the distribution of maternal serum AFP values in MoM in normal pregnancies (△–△) and in pregnancies associated with a Down's syndrome fetus (●–●).

0·186). The 95% confidence interval of the 86 affected pregnancies based on these values is shown in Fig. 1, the median was 0·64 MoM.

Probability plots of the distributions of the MoM-values on a log scale for the normal pregnancies and for the 86 affected pregnancies are shown in Fig. 2. It is seen that both distributions are very well described by normal distributions, i.e. correspond to straight lines in the probability plot.

In the women with a Down's syndrome fetus there was no correlation between the MoM value and age, and there was no significant difference between the cases detected by amniocentesis and those detected at birth. The empirical standard deviation (0·186) for the Down's syndrome pregnancies was not significantly higher than that for normal pregnancies (0·168).

However, in the risk calculations in the present study the estimate for each was used. Almost the same results are obtained if the standard deviation for the normal pregnancies are taken to be the true value also for the affected pregnancies.

The risk calculations were based on the following relations: Let x denote the value of log MoM, $f(x)$ the probability density of x related to normal pregnancies, $g(x)$ the probability density related to Down's syndrome pregnancies and $q(x) = f(x)/g(x)$ the ratio between these two densities. Furthermore, let a denote the probability *a priori* (depending on age) for Down's syndrome. Using Bayes' formula we get the following conditional probability:

$$p(DS/x) = a\,g(x)/(a\,g(x) + (1-a)\,f(x))$$
$$= a/(a + (1-a)\,q(x))$$

expressing the risk for a Down's syndrome pregnancy corresponding to a certain maternal age with probability a for Down's syndrome and an observed value of log MoM equal to x. Assuming $f(x)$ to be a normal distribution with mean value = 0 and SD = s_n and $g(x)$ to be a normal distribution with mean value = m and SD = s_d, and by introducing $c = s_d/s_n$ we get

$$q(x) = c\ \exp((x\text{-}m)^2 - c^2x^2)/2s_d^2)$$

It is seen that if $c = 1$ (the same SD in both distributions) this formula simplifies to

$$q(x) = \exp((m^2 - 2\,xm)/2s^2)$$

In our case $s_n = 0{\cdot}168$, $s_d = 0{\cdot}186$, $m = -0{\cdot}1972$ and $c = 1{\cdot}10714$.

The a-values used are shown in Table 1. They are based on the data (age-related risks in 5-year age groups from a number of studies) given in Table 3·2 by Stene & Mikkelsen (1984), transformed by a smoothing procedure into a continuous curve. Essentially the same results were obtained when similar calculations were made using maternal age-specific rates of chromosome abnormalities given by Hook (1981).

Based on these estimations, we calculated which combinations of maternal age and maternal serum AFP level resulted in a probability of having an affected infant high enough to warrant amniocentesis. We chose the probability of 1:400 as lower limit for referral for amniocentesis, as this corresponds to the risk in the youngest women (35 years of age), offered amniocentesis on account of maternal age in this country (Stene & Mikkelsen 1984).

Our calculations were applied to the Danish birth distribution by maternal age for 1983. The total number of births was 51 086 that year and the expected number of infants with Down's syndrome was 62·3.

The number of Down's syndrome fetuses found by amniocentesis, if all women with a risk above 1:400 were investigated, is shown in Table 1, which also shows the maternal serum AFP levels which for a given age resulted in a probability of having a Down's syndrome infant equal to 1:400.

These maternal serum AFP levels are used in Fig. 1 to give an iso-risk curve. In the four quadrants of this figure, the summed number of pregnancies (P) and the summed number of expected

Table 1. Number of fetuses with Down's syndrome (DS) detected in women referred for amniocentesis because of an estimated risk above 1:400, based on age and maternal serum alpha-fetoprotein (MSAFP) (expressed as MoM)

Maternal age at conception (years)	Age-related risk	MSAFP equal to a DS risk of 1:400	Proportion of women screened, using this cut-off	Proportion of DS fetuses found using this cut-off	Number of births in Denmark in 1983*	Estimated number of women referred for amniocentesis according to a 1:400 iso-risk curve	Estimated number of DS fetuses at each maternal age	Estimated number of detected DS fetuses according to a 1:400 iso-risk curve
18	1:1587	0·495	0·03459	0·28057	955	33	0·6	0·2
19	1:1562	0·497	0·03554	0·28429	1197	43	0·8	0·2
20	1.1538	0·500	0·03649	0·28799	1859	68	1·2	0·3
21	1:1493	0·504	0·03841	0·29530	2536	97	1·7	0·5
22	1:1449	0·509	0·04037	0·30250	3105	125	2·1	0·6
23	1:1408	0·513	0·04235	0·30960	3413	145	2·4	0·8
24	1:1333	0·522	0·04639	0·32347	3889	180	2·9	0·9
25	1:1266	0·530	0·05052	0·33693	4336	219	3·4	1·2
26	1:1190	0·540	0·05582	0·35321	4409	246	3·7	1·3
27	1:1099	0·554	0·06344	0·37503	4208	267	3·8	1·4
28	1:1031	0·565	0·07014	0·39289	3928	276	3·8	1·5
29	1· 943	0·581	0·08044	0·41833	3458	278	3·7	1·5
30	1: 870	0·597	0·09099	0·44225	2991	272	3·4	1·5
31	1: 775	0·619	0·10778	0·47675	2372	256	3·1	1·5
32	1: 685	0·645	0·12861	0·51473	1950	251	2·8	1·5
33	1: 581	0·682	0·16094	0·56573	1636	263	2·8	1·6
34	1· 490	0·723	0·20079	0·61890	1311	263	2·7	1·7
35	1: 398	0·778	0·25819	0·68226	1034	267	2·6	1·8
36	1. 319	0·844	0·33008	0·74634	805	266	2·5	1·9
37	1: 248	0·930	0·42564	0·81351	550	234	2·2	1·8
38	1: 195	1·024	0·52396	0·86747	409	214	2·1	1·8
39	1: 157	1·122	0·61685	0·90803	337	208	2·2	2·0
40	1: 118	1·276	0·73563	0·94837	165	121	1·4	1·3
41	1: 88	1·466	0·83885	0·97465	100	84	1·1	1·1
42	1: 61	1·784	0·93266	0·99204	55	51	0·9	0·9
43	1: 45	2·170	0·97736	0·99793	33	32	0·7	0·7
44	1: 32	2·815	0·99626	0·99974	46	46	1·5	1·5

* Based on The Statistical Department (1984).

Down's syndrome cases (D) for women above or below the iso-risk curve, and for women above or below 35 years of age are shown.

The performance of the screening factor used for referral for amniocentesis to detect Down's syndrome in the fetus was calculated from the data shown in Fig. 1. When maternal age ≥35 years was used to select women for amniocentesis, the sensitivity, that is the proportion of Down's syndrome cases detected, was (14·8+2·5):62·3 = 0·277, and the specificity, that is the proportion of all pregnant women considered to be at low risk, was (44 271 +3282):51 086 = 0·93. The overall risk of having an infant with Down's syndrome in women ≥35 years of age would be (2·5+14·8):(2010+1523) = 0·0049 (predictive value of a positive 'test', i.e of being ≥35 years of age). Thus, if maternal age was used as the only criterion for referral for amniocentesis, amniocentesis in 6·9% [(2010+1523):51 086] of all women would detect 27·7% of the fetuses with Down's syndrome.

If women were selected for amniocentesis on the basis of the (1:400) iso-risk curve, the sensitivity would be (18·2+14·8):62·3 = 0·53 and the specificity (44 271+2010):51 086 = 0·91 The risk of having an affected infant if selected for amniocentesis by this iso-risk curve would be (18·2+14·8):(3282+1523) = 0·0069. If the iso-risk curve was used for referral for amniocentesis, amniocentesis in 9·4% [(3282+1523).51 086] would detect 53% of the fetuses with Down's syndrome.

Discussion

The present study confirmed that the level of maternal serum AFP can be used as a predictor of risk for Down's syndrome. By combining this factor with the presently-used screening factor, namely maternal age, we have constructed an iso-risk curve for the whole pregnant population, i.e. a curve showing which combinations of the two factors yield a particular risk of Down's syndrome. We chose 1 in 400 as the lowest risk of Down's syndrome warranting referral for amniocentesis, as this corresponds to the risk of the youngest women (35 years) presently offered amniocentesis because of advanced maternal age (Stene & Mikkelsen 1984). However, similar curves can be constructed for any other chosen risk. If an iso-risk curve is used to screen the whole population instead of maternal age alone, the screening performance of the referral factor for amniocentesis is improved: the sensitivity is doubled (0·28 to 0·53) and the specificity loss is small (0·93 to 0·91). In other words, the detection rate of Down's syndrome is increased from 28 to 53% by referring 9·4% of women for amniocentesis according to the iso-risk curve instead of the 6·9% aged ≥35 years. Because genetic amniocentesis is performed on other indications than maternal age, the number of Down's syndrome fetuses detected at present is higher than the expected 28%, but this would probably also be the case, if an iso-risk curve was used to select women for amniocentesis

The high detection rate obtained by using our iso-risk curve is partly due to the low median maternal serum AFP in pregnancies affected with Down's syndrome (0·64 MoM) found in the present study. Other studies including 40–61 affected pregnancies have reported slightly higher levels (0·63–0·80 MoM) (Cuckle *et al.* 1984; Murday & Slack 1985; Fuhrmann *et al.* 1984), and if the median level of maternal serum AFP in affected pregnancies is shifted towards the median level in chromosomally normal pregnancies, the detection rate of Down's syndrome fetuses will decrease.

Only 10% of the women who later gave birth to infants with Down's syndrome had a serum AFP determination. This is slightly less than would have been expected, as the serum AFP screening programme covered approximately 14% of the Danish pregnant women. However, the age distribution of pregnant women in the counties participating in the serum AFP screening programme was not different from the age distribution of all pregnant Danish women (National Health Board 1985) and, as far as we know, none of the women who had a Down's syndrome baby in the regions screened had missed the blood test. Thus, there does not seem to be any bias in the selection of the cases in the present study.

On the basis of the same two screening factors, Cuckle *et al.* (1984) proposed a different selection strategy for amniocentesis based on maternal age-specific serum AFP cut-off levels for women between 25 and 37 years of age. Irrespective of the level of maternal serum AFP, all women above 37 years, but none of those below 25 years, were offered amniocentesis. With this strategy, 40% of affected pregnancies and 6·8% of unaffected pregnancies were selected for amniocentesis in their population, where the median maternal serum AFP in affected pregnancies was 0·72 MoM. The strategy suggested by Cuckle *et al.* (1984) gives a higher yield (1 case of Down's syndrome per 102 amniocenteses) than ours using the 1:400 iso-risk curve (1 case of Down's syndrome/156 amniocenteses). This may be explained by Cuckle *et al.* (1984) suggesting a policy which identifies pregnancies further into the tail of the age and maternal serum AFP distribution, i.e. a higher combined age and AFP cut-off level. Another reason for the higher yield of that policy could be because in their selected population the prevalence of Down's syndrome was 1·4 times higher than in our estimated data for the whole Danish population. Murday & Slack (1985) applied the same screening strategy (Cuckle *et al.* 1984) in the North East Thames population, where women aged ≥38 years are offered amniocentesis. The smallest risk of Down's syndrome that warranted referral for amniocentesis in this region was therefore 1 in 200. They found that the sliding scale (Cuckle *et al.* 1984) was only useful in women aged ≥32 years, as no younger woman was found to be at a greater risk than 1 in 200, no matter how low her serum AFP was. Our strategy of selection for amniocentesis differs from the one proposed by Cuckle *et al.* (1984) on a major point. Using our strategy all women, irrespective of their age, will be referred for amniocentesis, if their risk of having a baby with Down's syndrome is ≥1:400. As can be seen from Fig. 1, a young woman with a low serum AFP level may have a greater risk of carrying a Down's syndrome pregnancy than an older woman with a high serum AFP level. Therefore, with our present knowledge, selection based on an iso-risk curve would give equal opportunity to all pregnant women. Our age-related risk of Down's syndrome was based on 10 studies from several countries (Stene & Mikkelsen 1984), including one from Denmark, but was evidently not done on the same population, at the same time, as the population studied in the present paper. However, data from an American study (Hook 1981) gave essentially the same results. The question is not whether the curve should be placed at a slightly higher or slightly lower level, but rather whether one wants to use such a curve to select women for amniocentesis. If so, it should also be decided which level of risk should be used and at which time in pregnancy. Due to the higher rate of late intrauterine death of Down's syndrome fetuses compared with chromosomally normal fetuses (Hook 1978), an iso-risk curve based on the prevalence of Down's syndrome early in the second trimester would be shifted upwards and to the left compared with an iso-risk curve based on the birth-prevalence of Down's syndrome.

Such an iso-risk curve may be difficult to understand for the individual woman and its application may create some problems, psychological for the women involved and organizational in the conduction of the screening. At present, women ≥35 years of age are offered amniocentesis and fetal chromosome analysis, a test with nearly 100% sensitivity for Down's syndrome and other chromosome abnormalities (Loft & Tabor 1984). If these women are offered amniocentesis on the basis of an iso-risk curve instead, 2·5 out of 17·3 Down's syndrome cases (Fig. 1) and a number of other chromosome abnormalities will not be diagnosed. On the other hand, by applying the iso-risk (1:400) curve in women <35 years of age, whose present access to amniocentesis is limited, almost half of the Down's syndrome fetuses, as well as a number of other chromosome abnormalities, would be detected in these younger women.

The risk of Down's syndrome should be considered in relation to the possible risks associated with the diagnostic procedure. In a randomized study of genetic amniocentesis in 4606 women, aged between 25 and 34 years, the risk of spontaneous abortion was 1·0% (95% confidence limits 0·3–1·5) (Tabor *et al.* 1986), and there is no reason to believe, that it should be lower in older women. This risk may well seem too high for women >35 years of age with high serum AFP levels and a subsequent risk of having Down's syndrome fetus around 1 in 1000 (Fig. 1). In other words, in this group of women, about 20 chromosomally normal fetuses would be spontaneously aborted to diagnose two Down's syndrome fetuses.

A screening policy based on an iso-risk curve would require greater resources. Even if it is possible to reduce the number of amniocenteses by ultrasound revision of gestational age (Cuckle *et al.* 1984), the amniocentesis rate will increase. In Denmark, a 10% amniocentesis rate would not be unacceptably high. The national yearly rate has been 10–11% since 1983 and therefore the cytogenetic resources are available. An increased level of maternal anxiety may be another important side-effect of such a programme (Seller 1984). By analogy with women with elevated serum AFP levels, the counselling about having amniocentesis in mid-pregnancy because of a then acknowledged risk may be more stressful than being referred for amniocentesis because of an *a priori* risk (Farrant 1980).

The acceptability of a screening based on maternal age and serum AFP level was found to be as high as 80% in women <35 years of age (Baumgarten *et al.* 1985), but the problem may be to introduce this screening policy in women >35 years of age, who are now all offered amniocentesis. There is no doubt that if the access of older women to amniocentesis were to be restricted, this would demand much public information and a great increase in genetic counselling capacity.

In conclusion, maternal serum AFP is not a diagnostic test for Down's syndrome, but serum AFP may be used in women of all ages in conjunction with the maternal age to estimate the likelihood that the pregnancy is associated with a Down's syndrome fetus.

Acknowledgments

This study has been supported by the Danish Medical Research Foundation (jr.nr. 512-10286 and jr.nr. 512-20064), Helsefonden (H 11/55-87) and the Dagmar Marshall Foundation.

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Received 8 September 1986
Accepted 12 December 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 643–648

Outcome of pregnancies progressing beyond 28 weeks gestation in women with a history of recurrent miscarriage

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Summary. Ninety-seven women who had had three or more miscarriages had also had at least one pregnancy with a singleton birth that had reached 28 weeks gestation. Information was available on these 118 babies: 30% were small-for-gestational age (birthweight ≤ 10th centile using figures from Scotland 1973–79), 28% were born preterm, and the perinatal mortality rate (excluding babies of <28 weeks gestation) was 161/1000 births, all of which are significantly increased above the prevalence for a normal obstetric population. These observations may serve to alert the clinician to the increased risk of these complications when dealing with women who have a history of recurrent miscarriage.

It has been suggested that women with a history of miscarriage tend to have babies that are preterm, small-for-gestational age and have an increased perinatal mortality (Schoenbaum *et al.* 1980; Funderburk *et al.* 1976; Pontelakis *et al.* 1973, Macnaughton 1961). In our population of women attending the recurrent miscarriage clinic we have observed that one third of them had had one or more pregnancies progressing beyond 27 completed weeks of gestation in addition to three or more miscarriages.

The purpose of this study is to determine the frequency of adverse outcomes such as small-for-gestational age, preterm delivery and perinatal death in these pregnancies. The influence of such factors as the sex of the babies, number of miscarriages, ordinal position of the viable birth and partner specificity on these outcomes has also been investigated.

Patients and methods

The study included 344 women, with a history of three or more miscarriages, who were seen in a special gynaecological clinic at the Samaritan Hospital for Women between March 1982 and August 1985. Information about obstetric history was obtained from these patients. The information was not verified from the case records of the many hospitals at which the pregnancies had been managed A past history of miscarriage was only accepted if the diagnosis of pregnancy had been made on ultrasound scan, a positive pregnancy test or on histology. Of these women, 61% had had only first trimester miscarriages (<13 weeks gestation), 36% had had a mixture of first and second trimester miscarriages and 3% had had only second trimester miscarriages. Nine women gave a history of termination of pregnancy in addition to three or

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more miscarriages. There were 97 women who had had, in addition to their three or more miscarriages, at least one singleton pregnancy which progressed to 28 weeks gestation. Their average age was 30 years (range 22–42) and the number of miscarriages ranged from 3 to 11 (mean 4·4). These 97 women had had 122 babies between them—74 one, 21 two, and two had had three babies, but complete information was only available on 118 babies; 72 of these 118 babies (61%) were born to mothers in whom the first pregnancy ended in a viable birth. The remaining 46 babies were born to mothers whose first pregnancy was a miscarriage and the viable birth occupied variable ordinal position in relation to the miscarriages.

Definitions

Miscarriage. This term has been used specifically to describe a pregnancy that has aborted spontaneously before 28 weeks gestation (190 days from the first day of the last menstrual period). The term 'miscarriage' is used in preference to abortion to distinguish clearly between 'spontaneous' abortion and other types of abortion such as 'induced' or 'legal' (Beard *et al.* 1985). Women who have had one or more pregnancies which have progressed to 28 weeks gestation or more in addition to having three or more miscarriages are defined as secondary recurrent miscarriers.

Small-for-gestational age (SGA). The definition of small-for-gestational age in our study is complicated by both the heterogeneity of origin of our study population and the fact that even in homogenous populations such as Aberdeen [from which Thompson *et al.* (1968) derived their birthweight-gestation charts] standards have changed. For this reason, while we have defined SGA as occurring when the birthweight falls below the 10th centile, we have used the latest figures from Scotland between 1973 and 1979 (Information Services Division, Scottish Health Service, quoted by Macfarlane & Mugford, 1984) to determine the numbers of SGA babies.

Preterm delivery. This is a birth occurring before 37 completed weeks gestation (259 days from the first day of the last menstrual period).

Perinatal motality rate (PNMR). This is expressed in Britain as the number of stillbirths and early neonatal deaths/1000 births. A stillbirth (SB) is a baby of ≥28 weeks gestation dying before delivery. Our retrospective data on neonatal deaths is difficult to analyse because of the uncertainty from the history as to whether a baby of <28 weeks gestation showed any sign of life, although we know that none of them survived. For this reason we have modified the definition of an early neonatal death (NND) to include only babies of ≥28 weeks showing signs of life at delivery and dying within the first week of life. This is used in preference to the present British definition which includes babies of any gestational age, with signs of life at delivery but dying during the first week after birth. This modification means that our PNMRs are, if anything, a little below the rate expected if the accepted British definition had been used.

Statistical methods

We have used 'relative risk' to compare our sample with routinely collected obstetric statistics. Wherever relevant, the significance of differences has been determined using the χ^2 test.

Results

Figures 1a and 1b are derived from the 1973–79 Scottish data and show the distribution of birthweight of the 118 babies relative to their sex and gestational age. It is evident that these babies tended to have lower birthweight than the reference population, with 72% being below the 50th centile and with all the perinatal deaths occurring in this weight range. Also using the Scottish data, Table 1 shows that the prevalence of SGA is 30%, representing a relative risk of 3 when compared with an unselected obstetric population. Preterm delivery occurred in 28% which represents a relative risk of 3·3 when compared with the rate of 8·5% in the Scottish data for the period between 1973 and 1979.

Overall 32 babies weighed <2·5 kg giving a frequency of low birthweight of 27% which is much greater than the 7% of 636 818 babies born in England and Wales in 1984 (OPCS Monitor DH3/85/3) and therefore the relative risk is 3·9.

There were 19 perinatal deaths among the 118 babies, a rate of 161/1000 births. This is considerably higher than the rates from England and Wales during the years in which these babies

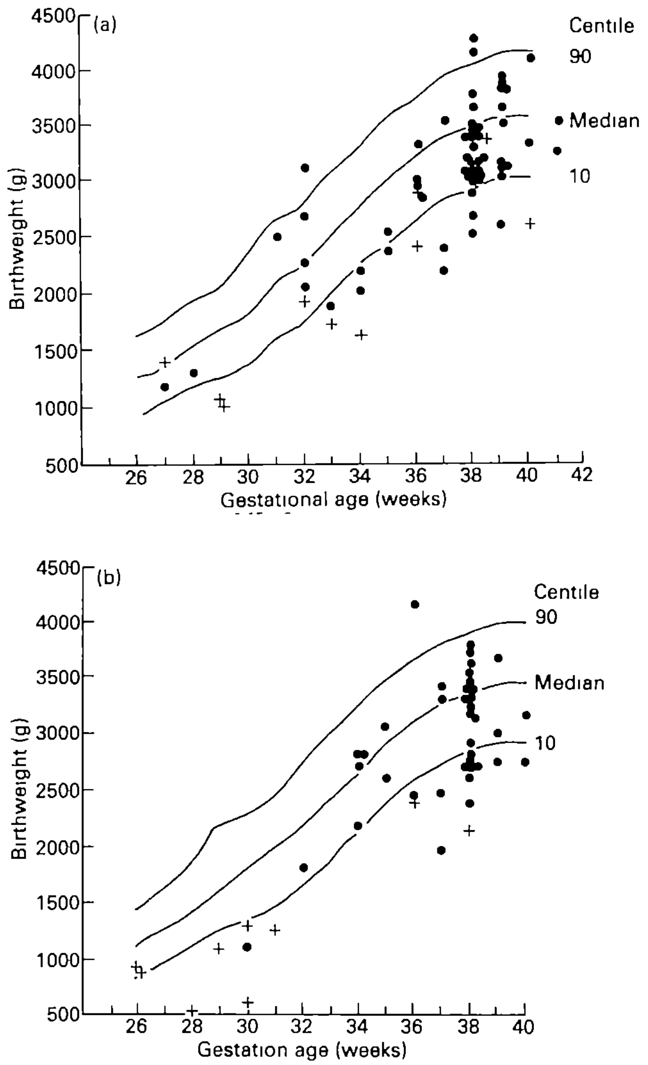

Fig. 1. Birthweight of male (a) and female (b) babies plotted on weight/gestation charts based on the Scottish figures 1973–79 (●) Survivor; (+) perinatal death

were born (OPCS 1975–84) when the perinatal death rate fell from 19·3 in 1975 to 10·1. This gives a relative risk of 15·9.

Sex of baby

Table 1 shows that there were more male than female babies in our sample and that this difference is statistically signficant ($\chi^2=4{\cdot}1$, $P<0{\cdot}05$ one sample test); 42% of the females were SGA compared with 23% of the males and this difference is signficant ($\chi^2=3{\cdot}9$, $P<0{\cdot}05$ with continuity correction). There was no significant difference in the PNMR or the rate of premature deliveries between the sexes.

Number of previous miscarriages

Table 2 shows that there is no significant difference in the frequency of SGA, preterm delivery and PNM between women who had had only three miscarriages and those who had had four or more.

Table 1. Frequency of small-for-gestation, preterm delivery and perinatal death amongst male and female babies of women with a history of recurrent miscarriage

	Total no.	Small-for-gestation*	Preterm delivery	Perinatal deaths		
				SB	NND	PNMR (‰)
Males	70 (59%)	16 (23%)	18 (26%)	3	7	142‰
Females	48 (41%)	20 (42%)	15 (31%)	6	3	187‰
Total	118 (100%)	36 (30%)	33 (28%)	9	10	161‰

SB, Stillbirth; NND, neonatal death; PNMR, perinatal mortality rate.
* Based on birthweight-gestation charts, Scotland 1973–79.

Table 2. Relation between number of miscarriages and frequency of small-for-gestation, preterm delivery and perinatal deaths

	No. of women	Small-for-gestation*	Preterm delivery	Perinatal deaths
≤ 3 miscarriages	53 (45%)	14 (26%)	13 (24%)	10 (188‰)
≥ 4 miscarriages mean 5·4 range 4–11	65 (55%)	22 (33%)	20 (31%)	9 (138‰)

* Based on birthweight-gestation charts, Scotland 1973–79.

Ordinal position

The ordinal position of the viable birth with respect to the miscarriage(s) had no effect on the frequency of SGA, preterm delivery or perinatal mortality.

Partner specificity

Nineteen women had had two partners by each of whom they had become pregnant. None of the pregnancies from the first partner had miscarried. Subsequently, with their second partner, 14 of the women had only miscarriages, while five women had had, in addition to three or more miscarriages, one pregnancy that progressed beyond 28 weeks gestation. Of the 29 babies from the first partner, 26 had birthweights within normal range and only three were SGA. The mean birthweights were 3489 (SD 423) g for the male babies and 3259 (SD 592) g for the female babies. Only two of these babies were preterm (36 weeks gestational age each), and there was only one perinatal death. The fact that these pregnancies and offspring from first partners were so normal, whereas with second partners they ended in miscarriages suggests that recurrent miscarriage may be a partner-specific condition.

Discussion

This study has clearly shown that the prevalence of SGA, preterm delivery and perinatal death is much higher among babies born to women who attended our clinic with a history of recurrent miscarriage than in the rest of the population. It could be criticized that the women in our sample are self selected for another pregnancy and therefore the sample is more likely to include miscarriers who had a poor outcome with their viable birth in the past. However, the results of our study support the findings of other authors undertaking more population-based studies that there is an increased risk to pregnancies preceding or following miscarriage(s) (Alberman *et al.* 1980; Funderburk *et al.* 1976; Schoenbaum *et al.* 1980). Hence our findings are unlikely to be the product of a quirk of selection. This is an important clinical observation revealing that the risk of pregnancy failure in the first two trimesters continues into the third trimester if the pregnancy is capable of continuing that long. It also seems likely that recurrent miscarriage and the high associated rate of fetal and neonatal morbidity is partner-specific. It was not possible to compare our results with other published work because we could not find a study with a comparable number of women who had had as many miscarriages.

There are studies of pregnancy following one or more miscarriages and there is general agreement that these women have a higher rate of preterm delivery (Pickering & Forbes, 1985; Schoenbaum *et al.* 1980). There is also agreement that there is an increase in the rate of preterm delivery if the women had two or more miscarriages as compared with only one (Keirse *et al.* 1978; Funderburk *et al.* 1976; Papaevangelou *et al.* 1973).

There is less agreement on the association between miscarriage and SGA. However, Alberman *et al.* (1980) showed that the mean birthweight of babies born before a miscarriage was lower than that of babies who are followed by another live birth. In addition they also found that the mean birthweight of babies born to women with a history of two or more miscarriages fell as the number of miscarriages experienced rose. Paradoxically, the mean birthweight of babies born after one miscarriage was unaffected. In their survey of 4000 women who had had one or more miscarriage, and at least one pregnancy that had passed 28 weeks gestation, Pickering & Forbes (1985) did not find an increased prevalence of babies with weights below the 10th centile. The authors commented that the discrepancy between their findings and those of Alberman *et al.* (1980) was perhaps due to the different populations studied. We suggest that another factor may also have been responsible. Pickering & Forbes (1985) have removed all stillbirths from their data which, on the basis of our data, undoubtedly will have significantly reduced the frequency of SGA babies.

The high perinatal mortality in our study of women with recurrent miscarriage is in keeping with the findings of Funderburk *et al.* (1976). We have no evidence of an increased frequency of congenital malformations amongst these babies as was suggested by Schoenbaum *et al.* (1980), who found that the frequency of malformation tended to rise with the number of miscarriages. Without exception, the deaths occurred amongst babies that were SGA and, usually, preterm, suggesting that placental insufficiency was the most likely cause of death. Funderburk *et al.* (1976) found that perinatal mortality increased with the number of miscarriages, but we did not observe this association in our study.

There may be a link between the morbidity in the babies of secondary miscarriers and their tendency to miscarry. In human placentation, non-villous trophoblast invades the maternal decidua to infiltrate the spiral arteries thereby enlarging these arteries to supply the growing conceptus (Boyd & Hamilton 1970; Pjinenborg *et al.* 1980). It has been suggested (Robertson *et al.* 1985) that this process is sometimes defective in women who miscarry. The defective placentation in early pregnancy may be the explanation for the tendency to miscarry and for the increased rates of perinatal death, SGA and preterm labour amongst our secondary miscarriers. This hypothesis is supported by the finding of Brosens *et al.* (1967) that half their SGA pregnancies were associated with an incomplete transformation of myometrial spiral arteries to fully developed uteroplacental arteries which could seriously impair the normal increase in placental perfusion required to meet the needs of the growing fetus. This may provide an explanation for the risk of pregnancy failure throughout intrauterine life that secondary miscarriers appear to have. This process of trophoblast invasion may well be immunologically determined (Robertson *et al.* 1985) which would explain the partner-specific nature of secondary recurrent miscarriage

Acknowledgments

The authors would like to thank Mrs Jane Wadsworth for her help with the statistical analysis and Miss Cynthia Knight and Miss Ruth Griffin for their help in the preparation of this paper.

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Received 22 April 1986
Resubmitted 28 October 1986
Accepted 10 March 1987

British Journal of Obstetrics and Gynaecology
July 1987, Vol 94, pp. 649–655

Defective haemochorial placentation as a cause of miscarriage: a preliminary study

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Summary. The morphology of the placental bed in idiopathic sporadic and recurrent miscarriages was studied and the findings correlated with the fetal chromosomal pattern where possible. Defective development of haemochorial placentation, which was not necessarily linked with fetal chromosomal abnormality, was seen in association with some miscarriages. These preliminary results, not previously demonstrated, strongly support the concept that miscarriages and pregnancies complicated by pre-eclampsia and/or small-for-gestational-age infants may be a continuum of disorders with a similar pathology in the placental bed.

Many factors are likely to be responsible for miscarriages, most of which are non-recurrent, and although chromosomal abnormalities are one of the most important, their reported occurrence in miscarriages is only about 50% (Boue *et al.* 1985). Furthermore, there is the occasional fetus with a chromosomal abnormality which is not miscarried but attains viability. Causes must be sought for the remaining 50% or more of miscarriages unassociated with chromosomal defects.

It has been suggested that defective placentation may be of crucial import in miscarriage (Robertson 1976; Robertson *et al.* 1985), but this idea has never been fully investigated. Haemochorial placentation is established in the placental bed where the two genetically dissimilar maternal and fetal tissues intermingle intimately. If defective placentation is an important factor underlying miscarriage, it would be expected to be found more frequently in those woman with a history of unexplained recurrent miscarriages. We therefore report what we believe is the first study of the pathology of the placental bed in recurrent miscarriages and in idiopathic sporadic miscarriages with correlation, where possible, with cytogenetic studies of the fetal tissues.

Materials and methods

Materials

Tissue from the placental bed was collected from two centres. Pregnancies of patients with a known history of recurrent miscarriage were monitored by weekly ultrasound scanning and human chorionic gonadotrophin (hCG) assays to assess the viability of their current pregnancies. When either an anembryonic pregnancy or an intrauterine death was diagnosed, these pregnancies were terminated using appropriate methods and placental bed tissue was obtained by curettage immediately before the termination. Under anaesthetic and with the patient's bladder full, an ATL Mk100 sector scanner was used to locate the decidua basalis. A small curette was guided under ultrasound control to the site where the placenta appeared to be localizing and several strips of tissue were taken to try to include the placental bed. This technique was used when the pregnancy was intact.

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Table 1. Clinical details of patients and summary of results

Patient no	Gravidity	Previous pregnancies	Gestational age (weeks)	Fetal chromosome	Uteroplacental circulation	Current pregnancy and comments
Comparison group						
1	1	—	9	46XY	D+	Induced abortion
2	1	—	8	ND	D+	Induced abortion
3	1	—	9	ND	D+	Induced abortion
4	7	SbMLMMM	16	46XX	D+M+	Miscarriage, live fetus, cervical incompetence
Study group						
5	1	—	9	46XX	?*	Missed miscarriage (anembryonic), sac still growing; scarce interstitial trophoblast
6	1	—	13	trisomy 10	D+	Missed miscarriage (anembryonic)
7	1	—	19	ND	D−M−	Missed miscarriage
8	3	LL	12	47XX+22	D+	Missed miscarriage (anembryonic), pregnancy with new partner
9	3	SbM	25	ND	D−M−	Missed miscarriage complicated by pre-eclampsia
10	4	LTM	10	47XY+15	D−	Missed miscarriage
11	4	MML	10	failed	D+	Missed miscarriage (anembryonic)
12	4	TMM	16	ND	D−†	Miscarriage; live fetus
13	5	TTMM	18	ND	D−M−	Miscarriage; live fetus
14	7	TLLMMM	9	46XX	D−	Missed miscarriage
15	8	MMMMMMM	16	46XY	D−M−	Miscarriage, live fetus
16	9	MMMMMMMM	10	46XY	D+	Missed miscarriage (anembryonic), sac still growing

ND, Not done; M, miscarriage; T, induced abortion; L, live-born; Sb, still-born.

D+/D−, Presence or absence, respectively, or physiological changes in decidual segments; M+/M−, presence or absence, respectively, of physiological changes in myometrial segements

* No maternal vessels seen in small biopsy

† No myometrial segments seen for comment.

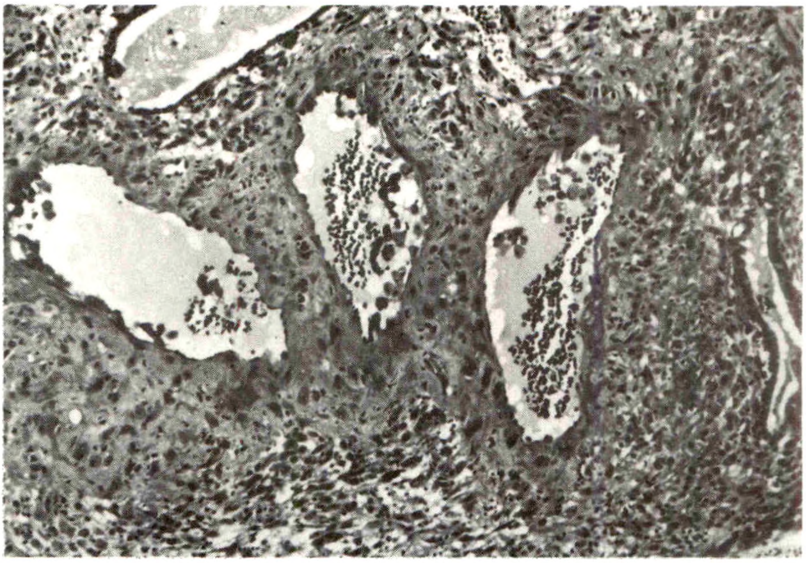

Fig. 1. Placental bed from a normal pregnancy at 8 weeks gestation (patient 2): the decidua basalis is overrun by interstitial trophoblast and three cuts through a spiral (uteroplacental) artery show physiological changes. HE × 75.

In incomplete miscarriages, strips of curettings were taken from several sites. Placental bed tissue was similarly obtained from patients undergoing induced abortions. Biopsies of the placental bed were attempted in 21 cases and proved on histological examination to be from the placental bed in 16 (76%).

Patients

The clinical details of these 16 women are listed in Table 1. Four of them constitute a comparison group comprising three patients having induced abortions with presumed 'normal' pregnancies and one patient who miscarried due to cervical

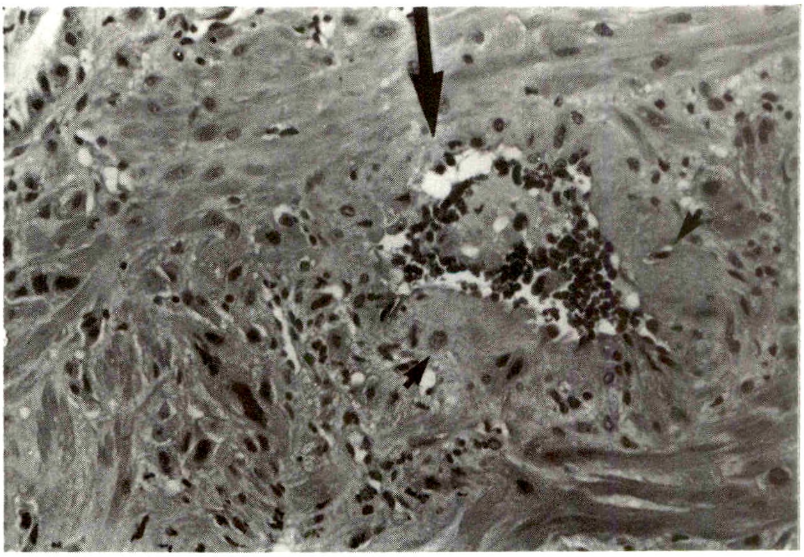

Fig. 2. Placental bed from a miscarriage at 16 weeks gestation as a result of an incompetent cervix (patient 4): a myometrial segment of a maternal uteroplacental artery showing (arrow) physiological changes with endovascular trophoblast embedded within its wall (small arrows) and surrounding interstitial trophoblast. HE × 190.

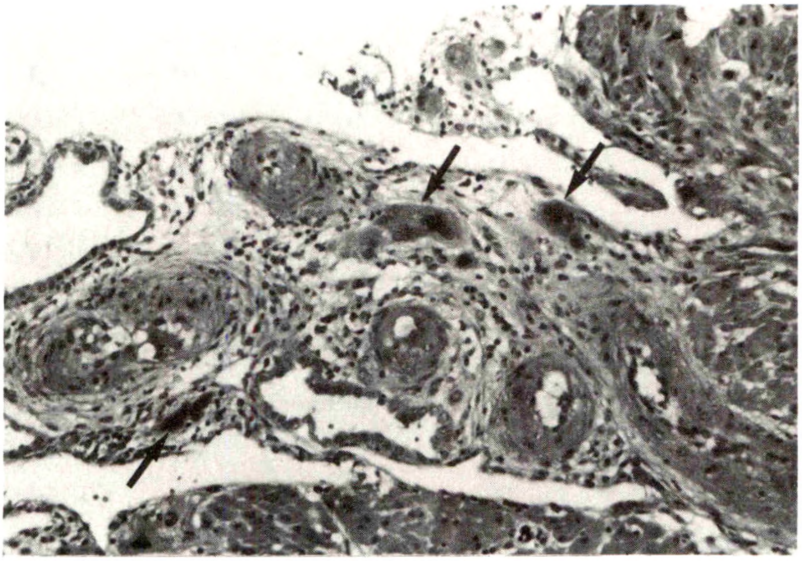

Fig. 3. Decidua basalis of a missed miscarriage at 10 weeks gestation (patient 10): a leash of maternal spiral arteries not showing any physiological vascular changes with resultant narrower lumens. Note placental bed giant cells (arrowed). HE × 120.

incompetence. The other 12 women constitute the study group and include women with recurrent miscarriages and those who miscarried for the first time, arranged in order of increasing number of previous miscarriages.

The placental bed tissue was placed in formal-saline and subsequently processed by standard methods. Sections were stained with haematoxylin and eosin (HE) and examined (T.Y.K. and W.B.R.) in ignorance of the clinical details.

Fetal tissues were submitted for culture for chromosomal analyses.

Results

Placental bed morphology

Comparison group. In each of the three induced abortions of apparently normal pregnancies during the first trimester, the placental bed showed normal development of the utero-placental vasculature with physiological changes in the decidual segments of all spiral arteries seen. The physiological vascular changes (Brosens *et al.* 1967) are characterized by a loss of the normal musculo-elastic tissue from the wall of the arteries and deposition of fibrinoid material in which endovascular trophoblast is embedded (Fig. 1). In the second trimester miscarriage due to an incompetent cervix, there was normal placentation with appropriate development of the uteroplacental (spiral) arteries in decidual and myometrial segments (Fig. 2).

Study group. There were seven missed miscarriages in the first trimester, two missed miscarriages and three miscarriages in the second trimester. In two first-trimester and all five second-trimester miscarriages, the utero-placental vasculature was inadequately developed in that some spiral arteries in the placental bed showed preservation of musculo-elastic tissue with no evidence of involvement with migratory extravillous trophoblast in the decidual segments in the first trimester miscarriages, and in the decidual and myometrial segments in second trimester miscarriages (Figs 3 and 4). Four of the other five first-trimester miscarriages had normally developed physiological changes in the decidual segments of the placental bed spiral arteries. In the remaining case no maternal spiral arteries were seen for assessment of the development of the uteroplacental vasculature but there was a paucity of migratory interstitial trophoblast in the decidua despite the presence of plentiful anchoring villi (Fig. 5). One woman (no. 9) had two earlier pregnancies that were complicated by pre-eclampsia and intrauterine death in the late second trimester. In her current pregnancy, acute atherotic lesions were seen in decidual segments of the spiral arteries (Fig. 6). Acute atherosis was not seen in

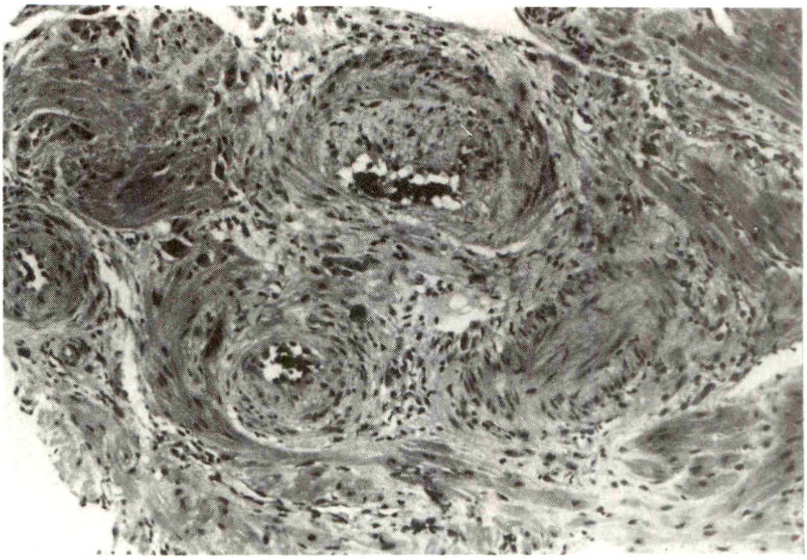

Fig. 4. Placental bed from miscarriage at 16 weeks gestation (patient 15): myometrial segments of spiral arteries without physiological vascular changes; surrounding interstitial trophoblast indicate placental bed. HE × 120.

the curetted material from the other patients in this category.

Chromosomal studies

Chromosomal analysis was successful in nine of the 10 attempts. There were three chromosomal abnormalities, one of which was associated with inadequate placentation. There was no correlation between the normality or abnormality of the chromosomal pattern and the normal development or otherwise of the uteroplacental vasculature. Although the numbers are too small for statistical analysis, it would appear that an abnormal uteroplacental vasculature is no more likely to be associated with chromosomally

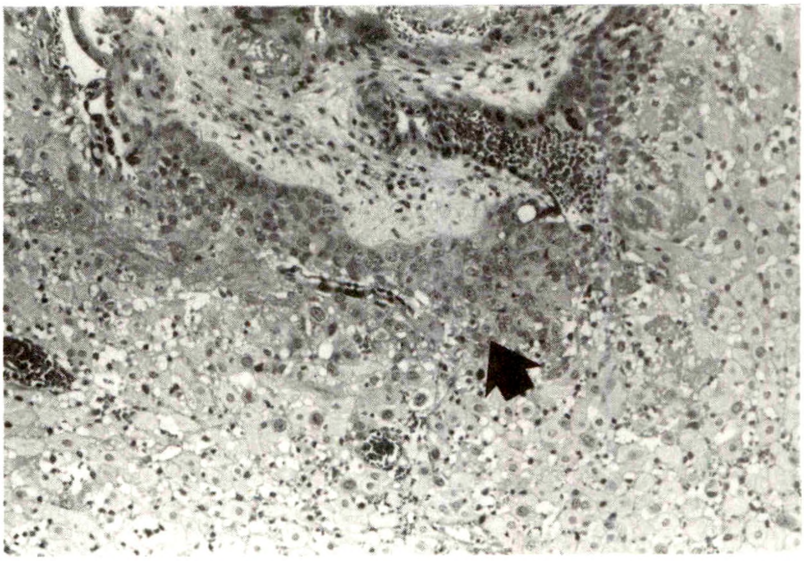

Fig. 5. Placental bed biopsy from missed miscarriage at 10 weeks gestation (patient 5): there is a paucity of migratory interstitial trophoblast in the decidua despite the presence of anchoring villi with a thick rim of cytotrophoblast (arrow). HE × 120.

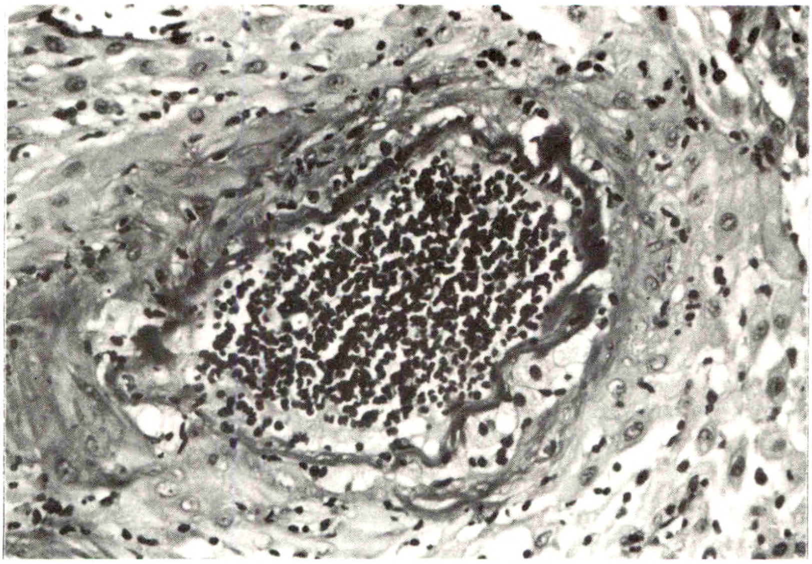

Fig. 6. Missed miscarriage at 25 weeks gestation which was complicated by pre-eclampsia (patient 9): acute atherosis is seen in a decidual artery. HE × 190.

defective fetuses than with chromosomally normal fetuses.

Discussion

The pattern of extravillous trophoblast migration and the temporal and spatial relation of spiral arterial changes in the placental bed of normal human pregnancy have now been well documented (Pijnenborg *et al.* 1980, 1981, 1983). Physiological vascular changes are normally well under way in the decidual segments of the spiral arteries by 8 weeks gestation and are completed in essentials by the end of the first trimester (Pijnenborg *et al.* 1980). Similar maternal vascular adaptations are normally initiated in the myometrial segments of the uteroplacental (spiral) arteries by 16 weeks gestation (Pijnenborg *et al.* 1983). We have used the findings of these studies as the pattern for normal pregnancies and this pattern of vascular changes was found in our three presumed normal pregnancies which were terminated and in the patient who miscarried at 16 weeks gestation apparently as a result of an incompetent cervix.

These vascular adaptive changes were not observed in two of the seven first-trimester and in none of the five second-trimester miscarriages in the study group, taking into consideration the expected vascular changes at the corresponding gestational ages when these miscarriages occurred. The argument that these adaptive changes would be present had the pregnancies proceeded longer is not tenable as the abnormal vasculature differed too much temporally and topographically from the normal. Nor is it valid to argue that there is no further development of the uteroplacental vasculature after death of the fetus because there is no longer a need for an increasing blood supply; the fetuses in three of the second trimester miscarriages were alive up to the time of the miscarriage, yet with inadequate maternal vascular adaptation.

The only apparent exceptions to the finding of an inadequate maternal vascular response to placentation were in four of the five missed miscarriages without apparent fetuses, the so-called anembryonic conceptuses. There are two possible explanations for this finding. First, such pregnancies if left alone would eventually be expelled from the uterus or, in a proportion of cases, evolve into molar or pseudomolar pregnancies and it is possible that had these four pregnancies continued into the second trimester that transformation of the myometrial segments of the uteroplacental arteries would not have occurred. Second, it is possible that only part of the developing placental bed is abnormally affected and, because only biopsy material was studied, 'false normal' findings are more likely than 'false abnormals' but this would be difficult to validate without hysterectomy specimens.

It is of interest that one of our patients developed pre-eclampsia as early as 25 weeks. The characteristic vasculopathy, acute atherosis, was seen in the biopsy but was noticeably absent in the other cases although the occurrence of this vascular lesion has been claimed in miscarriages by other authors (Nadji & Sommers 1973; Lichtig *et al.* 1985).

Our present study has demonstrated defective haemochorial placentation in association with miscarriage, whether of the recurrent or the sporadic type. Inadequate haemochorial placentation has been documented also in pregnancies complicated by pre-eclampsia and by small-for-gestational-age (SGA) infants (Brosens *et al.* 1972; Khong *et al.* 1986) indicating that all these pregnancy disorders share a common morphological feature in the placental bed and constitute a continuum of pregnancy failure (Redman *et al.* 1984; Reginald *et al.* 1987). However, the aetiologies of miscarriage, pre-eclampsia and SGA infants and the pathogeneses of a common form of defective placentation may differ. Insofar as miscarriage is concerned, it would seem that a failure of accommodation between the two genetically dissimilar tissues could be a potent factor in precipitating the catastrophe. Whether defective haemochorial placentation or a chromosomal abnormality is the more important factor in the aetiology of miscarriage remains to be determined but it is possible that they have a synergistic or an additive effect.

Acknowledgments

We wish to thank Professor R. W. Beard for his critical review of the manuscript and encouragement. The support of Birthright (T.Y.K. and H.S.L.) and the Medical Research Committee of St George's Hospital Medical School (T.Y.K.) are acknowledged

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Received 12 August 1986
Accepted 18 November 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol 94, pp. 656–664

Low human fetal heart rate variation in normal pregnancy

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Summary. The fetal heart rates of 340 normal singleton pregnancies at 30–33 weeks gestation were screened using a microprocessor system on-line. Eleven fetuses (3·2%) with a heart rate variation less than the 5th centile were identified, of whom 10 were studied longitudinally. At 30–33 weeks the mean minute range of pulse intervals (a measure of fetal heart rate variation) was 31·4 (SE 1·5) ms compared with 51·0 (SE 3·4) ms in a randomly selected control group. The study group continued to have significantly lower fetal heart rate variation than controls on each of three subsequent occasions until delivery. There were no significant differences between the two groups in fetal outcome, which was good. This demonstrates that a small proportion of normal fetuses have consistently low heart rate variation, and helps to define the lower limit of the normal distribution of fetal heart rate variation. After delivery, there were no significant differences between heart rate or its variation between the two groups. We conclude that the lower prenatal heart rate variation in the study group was a consequence of the uterine environment.

The pattern of the human fetal heart rate (FHR) is used as an index of well-being before and during labour. High heart rate variation is regarded as a sign of fetal health (Hon & Quilligan 1968; Hammacher *et al.* 1968), and reduced variation as an indication of compromise due to poor placental function. Computer-analysed FHR records have demonstrated the association between reduced heart rate variation and intrauterine growth retardation, in an in-patient population with a high incidence of pre-eclampsia (Henson *et al.* 1983, 1984).

However, there is a poor correlation with fetal outcome when the heart rate records with the lowest variation are selected from a general (i.e. mainly low-risk) obstetric population. In a previous screening study of 634 women with singleton pregnancies at 32 weeks gestation we showed that most (63%) of the cases with the lowest heart rate variation continued with an uneventful pregnancy and had a normal fetal outcome (Lawson *et al.* 1984). There are several possible explanations for these findings.

Firstly, the records in these 30 cases were of 45 min duration. Normal fetuses exhibit rest/activity cycling behaviour (Timor-Tritsch *et al.* 1978; Junge 1979; Nijhuis *et al.* 1982), and heart rate variation is reduced during the rest phase, which can last for up to 40 min (Visser *et al.* 1982). It is possible that in these cases the record happened to coincide with a resting phase, and was too short to measure accurately the overall heart rate variation.

Secondly, there may be longer-term fluctuations in the heart rate variation of the same fetus, so that in a large sample some records are unrepresentative.

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Thirdly, it is possible that some fetuses normally have relatively low heart rate variation throughout pregnancy. This individual pattern would be susceptible to the influences of increasing gestation (Wheeler *et al.* 1979; Dawes *et al.* 1982*b*) and superimposed pathology, for example placental dysfunction due to pre-eclampsia. By this concept the fetus can have 'normally low' heart rate variation, just as an infant with a birthweight below the 10th centile for sex and gestation can be 'normally small', without evidence of placental dysfunction or other pathology (Ounsted & Ounsted 1973; Jones & Roberton 1984).

In order to clarify these issues, we have undertaken a second study of screening FHR variation at 32 weeks, but with a protocol differing in three respects. First, the maximum length of record was extended to 60 min. Secondly, the study was restricted to normal pregnancies. And thirdly, those with the lowest FHR variation (less than the 5th centile) were studied longitudinally, that is, at 30–33 weeks gestation, on three subsequent occasions before birth and again soon after birth, and compared with randomly selected control subjects.

Subjects and methods

A two phase study was designed to identify and then investigate longitudinally those fetuses with the lowest heart rate variation. Women with normal singleton pregnancies of between 30 and 33 weeks gestation, who were attending the antenatal clinic at the John Radcliffe Hospital, Oxford, were invited to participate. They were recruited only if no abnormalities of past medical or obstetric history were found after examination of the case notes, and if the present pregnancy was uncomplicated. Gestational age was calculated on the basis of either reliable menstrual dates or an ultrasound measurement of the biparietal diameter before 20 weeks gestation.

Recording methods and analysis

FHR records were made using a Hewlett-Packard 8040A Doppler ultrasound heart rate monitor, with a compact wide-range transducer (15245A), a maternal abdominal tocodynamometer (15248A) and an event marker (15249A) to identify fetal movements. The subject was in a reclining (not supine) position; no episodes of supine hypotension were identified.

The heart rate measurements were fed into a small pre-processor unit (based on a 6502 chip), together with the signal from the tocodynamometer and the event marker. The pulse intervals were digitized, subjected to an error algorithm (Dalton *et al.* 1977) and the valid values averaged over 1/16th min. The output from the pre-processor was fed to a Nascom 2 microprocessor for analysis on-line (Wickham *et al.* 1983; Dawes *et al.* 1985). Records were analysed every 5 min from 10 to 30 min, and every 10 min thereafter up to 60 min. During analysis a baseline was fitted to the heart rate record (Dawes *et al.* 1982*a*). The range of mean pulse intervals about the baseline was calculated minute by minute, excluding data from decelerations (>10 beats/min and 1 min), and was averaged to give a measure of heart rate variation (mean minute range in ms). Accelerations and decelerations of pre-defined size were identified. The basal heart rate was defined as the mean baseline heart rate in episodes of low FHR variation (see below), or, if there was no such variation, as the mean for the whole record. Baseline variation was calculated as the maximum pulse interval deviation of the baseline in ms. Each 1/16th min epoch was defined as containing a fetal movement or not, depending on whether the subject had pressed the event marker. The fetal movement rate/h was calculated for the complete record.

Episodes of high or low heart rate variation were defined when 5 out of 6 successive minutes or more had a range of pulse intervals greater than 32 or less than 30 ms, respectively. This threshold was set empirically from previous experience (Dawes *et al.* 1981, 1982*b*; Henson *et al.* 1984). The number of minutes of high and low variation during each record was calculated, and also the mean range and fetal movement rate during these episodes.

The heart rate records were of good quality, with a mean signal loss of 4·0% or less at each gestation.

Study design

The screening protocol was designed to minimize recording time, but to identify the 5% of fetuses with the least variation (Lawson *et al.* 1984). The records were stopped after 10 min if the mean range was 35 ms or more, after 20 min if 30 ms or more and after 30 min it 27 ms or more. These thresholds were derived from previous studies, expecting to remove cumulatively 75%, 90% and 95% of subjects with the higher heart rate variation respectively. If the mean range was less than 27 ms at the 30 min analysis, the subject was asked if she would take part in the second phase of the study. The remainder were not studied further.

If the subject agreed to continue in the study, the FHR record was continued for a total of 60 min. Arrangements were made to repeat the FHR record, if possible, on three future occasions. Thus the four gestational study periods were 30–33, 34–35, 36–37 and >37 weeks. The FHR records were performed at the same time of day on each occasion, if possible, in order to standardize for diurnal variation (Visser *et al.* 1982), but no attempt was made to standardize for rest/activity cycling behaviour—the FHR record was begun as soon as a good signal was obtained.

For each study subject, a control subject at the same gestation was picked at random from the normal population, and asked to take part in the study protocol. FHR records were not made available to the clinical staff involved in the subject's antenatal care, in order not to introduce bias in management. Clinical details of fetal outcome were noted and, if possible, umbilical cord gas values were obtained at delivery from a double-clamped segment of cord.

Finally, a neonatal heart rate record was obtained between 24 and 48 h after delivery, at the same time of day as the previous records. ECG signals from standard neonatal chest electrodes were passed to the Hewlett-Packard 8040A monitor and the analysis system on-line The records were started 1–2 h after a feed, and the infants almost always slept throughout the 60 min record. Neonatal movements were recorded by an observer, using the same event marker that was used by the mother antenatally. When heart rate signals detected by ultrasound and direct ECG are compared, there is good correlation between indices of FHR variation, excluding absolute beat-to-beat variation which was not used in this study (Lawson *et al.* 1983). All results are given as means (SE) and are analysed statistically using the paired Student's *t*-test and the non-parametric Mann–Whitney test.

Results

Of 340 women screened between 30 and 33 weeks gestation, 11 fetuses (3·2%) were identified with a mean minute range less than 27 ms after 30 min of recording. Table 1 shows the frequency distribution of records by length, using the criteria for selection. The mean length of record in those not taking part in the second part of the study was 13·3 min. Of the 11 women identified, one was unable to take part in the second phase of the study, but details of fetal outcome were available, and are included in the results.

FHR analysis at 30–33 weeks gestation

FHR variation (mean minute rate) in the study group was significantly lower after both 30 and 60 min recording, than in the control group (Table 2). When the second 30 min alone was analysed, the difference was still significant. There was no significant difference in basal heart rate or baseline variation between the two groups. There were fewer accelerations in the study group, when the records were analysed over the first 30 min or 60 min; the difference was not significant over the second 30 min. The fetal movement rate in the study group during the first 30 min was significantly lower than in the control group. Over the second 30 min, or over the whole 60 min, the difference between the groups was not significant.

The first and second 30 min of the records within each group were compared, to examine if fetal cycling behaviour was giving a biased sample in the first 30 min. The only difference within the control group was a fall in the basal heart rate. In the study group there were significant increases in the FHR variation (mean range), the number of accelerations and the fetal movement rate in the second half of the record. Basal heart rate did not change. Thus there was evidence that the low FHR variation at 30 min was in part attributable to fetal rest/activity cycles; nevertheless, the second more reactive halves of the study records were significantly less variable than the control records.

Using a 30–32 ms threshold for the identification of episodes of high and low heart rate variation, there was less time spent in high variation and more time in low variation in the study group than in the control group (Table 3). The mean minute range in high variation was lower in the study than in the control group.

Table 1. Frequency distribution of 340 records by record length

Length of record (min)	Mean minute range criteria (ms)	Records		Cumulative percentage	
		n	%	Observed	Expected
10	>35	244	71·8	71·8	75
20	>30	60	17·6	89·4	90
30	>27	25	7·4	96·8	95
30	<27*	1	0·3	97·1	95
60	<27	10	2·9	100	100
Totals		340	100	100	100

* One subject with a mean range <27 ms at 30 min who was unable to take part in the second phase of the study.

Table 2. Fetal heart rate analysis at 30–33 weeks gestation

Variable	Study (*n* = 10)	Control (*n* = 10)	*P* value (study/control)
0–30 min			
Mean range (ms)	24·0 (1·1)	51·0 (4·3)	<0·001
Basal heart rate (beats/min)	143·9 (2·2)	140·5 (1·8)	NS
Fetal movement rate (moves/h)	15·6 (5·1)	43·4 (9·6)	<0·02
Accelerations (>10 beats/min for 15 s)	1·1 (0·3)	6·7 (1·2)	<0·002
31–60 min			
Mean range	37·7 (2·7)†	51·8 (3·0)	<0·05
Basal heart rate	145·5 (3·1)	138·2 (1·5)*	NS
Fetal movement rate	89·4 (38·1)†	43·6 (9·1)	NS
Accelerations	5·7 (1·2)*	8·1 (1·2)	NS
0–60 min			
Mean range	31·4 (1·5)	51·0 (3·4)	<0 001
Basal heart rate	144·1 (2·2)	139·1 (1·6)	NS
Fetal movement rate	52·6 (18·8)	43·6 (7·1)	NS
Accelerations	7·0 (1·2)	15·2 (2·4)	<0·05

Results are means (SE).
Significance of within-group comparison of 0–30 and 31–60 min: †*P*<0·005; *<0·05.

Table 3. Duration of and mean range during episodes of high and low FHR variation

Gestational age (weeks)		High variation		Low variation	
		Study	Control	Study	Control
30–33	Duration (min)	14·7 (3·0)	38·7 (3·3)***	23·6 (4·0)	2·8 (1·3)***
	Mean range (ms)	46·2 (1·7)	57·0 (2·7)**	20·2 (1·0)	25·6 (3·5)
34–35	Duration (min)	23·9 (3·7)	37·1 (4·1)*	12·7 (4·4)	4·7 (3·6)*
	Mean range (ms)	52·8 (3·0)	61·0 (2·4)	19·9 (1·0)	25·8 (1·2)**
36–37	Duration (min)	13·3 (5·1)	42·5 (3·3)**	18·4 (5·0)	1·0 (1·0)**
	Mean range (ms)	51·2 (3·4)	63·7 (2·4)**	19·9 (1·2)	21·3 (1·3)
>37	Duration (min)	28·4 (2·8)	32·4 (4·7)	13·6 (2·5)	6·8 (3·0)
	Mean range (ms)	57·5 (5·8)	63·8 (4·8)	18·8 (1·5)	18·9 (1·0)

Results are means (SE).
**P*<0·05; ***P*<0·01; ****P*<0·005.

FHR analysis at 34–35, 36–37 and >37 weeks gestation

It was not possible to study every fetus in each gestational period; some women were unable to come to the John Radcliffe Hospital on more than two occasions before delivery, and three records were lost through computer failure.

The 60 min mean range in the study group remained significantly lower at all gestational ages when compared with the control group (Fig. 1). The basal heart rate was always higher in the study group, but the difference was only statistically significant at 36–37 weeks (Fig. 2). The number of accelerations continued to be lower than in the control group, but the differences were not statistically significant (Table 4). The fetal movement rates overall were moderately but not significantly higher in the study group (Table 4). There were no differences in baseline variation at any gestational age.

Using a 32–30 ms threshold, the study group spent less time in high and more time in low FHR variation at every gestational age, when compared with the control group (Table 3). The differences were significant at 34–35 and 36–37 weeks, but not at >37 weeks. During such episodes of high and low FHR variation, the mean range was consistently lower in the study group, although the differences were only significant for high variation at 36–37 weeks and for low variation at 34–35 weeks.

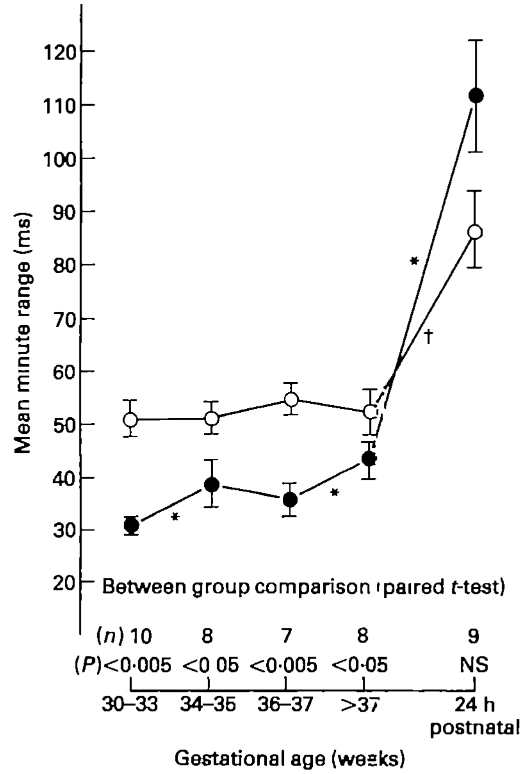

Fig. 1. Fetal heart rate variation (as the mean minute range over the full 60 min record). Within group comparison (paired Student's *t*-test) *$P<0{\cdot}05$; †$P<0{\cdot}001$. (●) Study; (○) control.

Longitudinal comparison within the control group showed no significant change in any variable of FHR analysis. In the study group, however, the 60 min mean range increased significantly from 30–33 to 34–35 weeks, and from 36–37 to >37 weeks (Fig. 1). Basal heart rate fell from 30–33 weeks to 34–35 weeks, and then rose to 36–37 weeks (Fig. 2). The fall in basal heart rate from 36–37 weeks to >37 weeks was not significant. There was a significant increase in the number of accelerations from 30–33 to 34–35 weeks, with no change thereafter (Table 4) and baseline variation also followed this pattern ($P<0{\cdot}01$). The fetal movement rate did not change (Table 4).

Figure 3 shows examples of a study and a control FHR record, both obtained at 34 weeks. Rest/activity cycling behaviour can be seen in both records, with similar fetal movement rates, but there is a two-fold difference in mean minute range over the whole record.

Although FHR variation in the study group was significantly lower than in the control group throughout pregnancy, the mean value for the 60 min mean range of the study group at each gestational age was significantly higher than that (20·6 SE 1·2 ms) of 21 fetuses before delivery by elective caesarean section for fetal compromise as adjudged by visual analysis of conventional FHR records (unpublished observations).

Fetal outcome

The study and control groups had similar fetal outcomes (Table 5). No babies were born by caesarean section; the seven vaginal operative deliveries were performed not for fetal distress but for failure to progress in the second stage of labour, or malposition of the fetal head. The umbilical artery gas values and Apgar scores in the control group were biassed by one baby born by Kjelland's forceps (for persistent occipito-posterior position), with pH 6·79, $P\text{co}_2$ 96·8, $P\text{o}_2$ 3·4, base excess −26.5 mmol and Apgar scores of 1, 5 and 7 at 1, 5 and 10 min, respectively. This

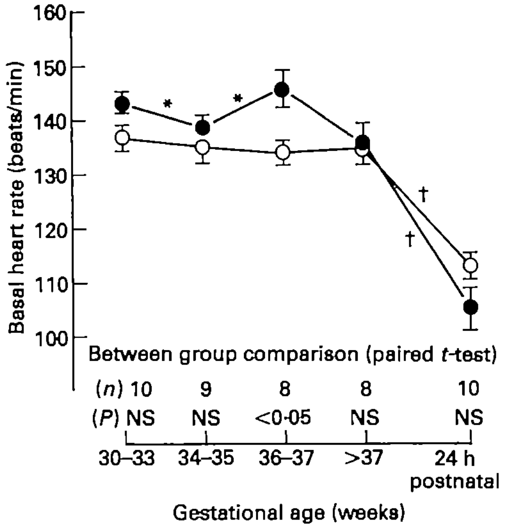

Fig. 2. Basal heart rate (beats/min). Within group comparison (paired Student's t-test) $^*P<0{\cdot}05$; $^\dagger P<0{\cdot}005$. (●) Study; (○) control.

baby was admitted to the special care nursery for 24 h for observation, but there was no evidence of neurological damage. All 21 babies were fit and well at discharge from hospital. There was a predominance of girls born in the study group ($P>0{\cdot}05$).

When the study group was divided into two halves, defined by the mean minute range in the *second* 30 min of the record at 30–33 weeks, and the two subgroups were compared for fetal outcome, there were no significant differences. There were no significant differences between the subgroups for any variable of FHR analysis at any later stage of pregnancy.

Neonatal heart rate analysis

All variables of heart rate analysis were similar in the study and control groups. The 60 min mean range in the study group was higher, and the basal heart rate lower than in the control group, but the differences were not significant (Fig. 1). In both groups there was a significant fall in heart rate and rise in heart rate variation (mean range) from the last record before delivery (Figs 1 and 2). There was no change in baseline variation or fetal movement rate.

Discussion

The screening criteria were based on a previous study (Lawson *et al.* 1984), where both normal and complicated cases were included, with the possibility of bias in the population towards lower FHR variation associated with pathological change. In the present study only normal pregnancies were screened, which may explain why only 3·2% of pregnancies with the lowest FHR variation were identified, whereas 5% were expected.

In the study group the mean range, number of accelerations and fetal movement rates were significantly higher in the second than in the first halves of the initial screening records, whereas this was not true in the control group. This suggests that the cases were selected partly on the basis of the resting part of the rest/activity cycle, and that the screening procedure introduced a bias. This was confirmed when the records at 30–33 weeks were compared with those at 34–35 weeks, and FHR variation and the numbers of accelerations were shown to increase significantly in the study, but not in the control group.

However, the bias was limited. When episodes of high variation were examined in the records at 30–33 weeks, the mean range was still reduced in the study group, and the overall FHR variation remained lower on each of three further occasions until full-term. Thus, we had

Table 4. Fetal movement rates and number of accelerations at all ages

Gestational age (weeks)	Fetal movement rate (moves/h)		Accelerations (>10 beats/min and >15 s)	
	Study	Control	Study	Control
30–33	52·6 (18·8) (n = 10)	43·6 (7·1) (n = 10)	7·0 (1·2) (n = 10)	15·2 (2·4) (n = 10)**
34–35	72·6 (15·9) (n = 9)	43·4 (11·3) (n = 9)	15·9 (3·6) (n = 9)*	19·3 (1·9) (n = 9)
36–37	55·5 (10·6) (n = 8)	46·8 (10·2) (n = 8)	14·3 (1·8) (n = 8)	20·0 (2·9) (n = 8)
>37	84·1 (26·7) (n = 7)	45·4 (13·4) (n = 7)	16·6 (2·0) (n = 7)	17·6 (3·1) (n = 7)
24 h postnatal	42·6 (6·9) (n = 10)	25·0 (9·0) (n = 8)	26·4 (3·4) (n = 10)	19·8 (3·4) (n = 8)

Results are means (SE), n is the number of records.
$^*P<0{\cdot}05$ (within the study group); $^{**}P<0{\cdot}02$ (between study and control groups).

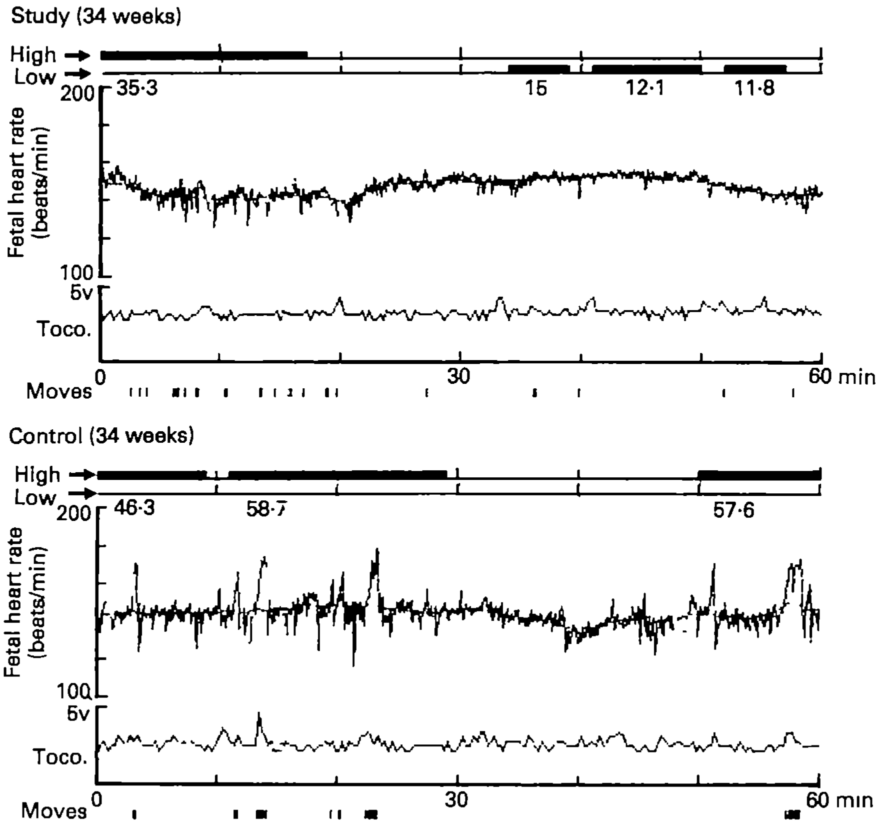

Fig. 3. Examples of study and control FHR records. The thick lines above the record denote episodes of high and low FHR variation (see text for definitions), with the mean range of pulse intervals (ms) during each episode given below.

	Study	*Control*
60 minute mean range (ms)	23·7	47·8
Basal heart rate (beats/min)	151	144
Fetal movement rate (moves/h)	28	34
Gestational age at delivery (weeks)	40	41
Mode of delivery	Spontaneous	Forceps
Birthweight (kg)	3·94	3·27
Final outcome	Alive and well	Alive and well

identified a group of fetuses with persistent atypically low FHR variation, that did not predict fetal compromise. We conclude that low FHR variation is a normal feature of some fetuses.

Differences in FHR variation could indicate differences in fetal rest-activity cycling behaviour. The mean minute ranges during episodes of high and low FHR variation in the study group were both lower than in the control group. On the other hand, the duration of high variation was shorter, and of low variation longer, in the study group when compared with the control group. But the differences were not always statistically significant. The fetal movement rates did not differ between the two groups at any gestational age (Table 4), suggesting that fetal behavioural states were similar, and not causing the differences in FHR variation (Visser *et al.* 1982). This suggests that the difference in FHR variation is due to a damping effect during both phases of rest/activity cycling behaviour, as in growth-retarded fetuses (Henson *et al.* 1984).

The difference in heart rate variation between the two groups did not continue into the neonatal period, although both groups showed a significant fall in basal heart rate and rise in the mean minute range. Thus the mechanism which

Table 5. Fetal outcome in study and control groups

	Study group ($n = 11$)	Control group ($n = 10$)
Birthweight (kg)	3·43 (0·18)	3·34 (0·15)
Gestation (days)	280 (2·4)	279 (3·2)
Centile for gestation/sex (%)	56 (10)	50 (8)
Sex		
Female	9	6
Male	2	4
Mode of delivery		
Forceps	2	5
Spontaneous vaginal	9	5
Apgar score		
1 min	8·6 (0·4)	7·3 (0·8)*
5 min	10·0 (0)	9·5 (0·5)*
Umbilical artery		
pH	7·266 (0·024)	7·170 (0·049)*
$P\text{CO}_2$ (mmHg)	47·4 (2·6)	55·3 (5·7)*
$P\text{O}_2$ (mmHg)	15·8 (2·8)	10·2 (1·8)*
ABE (mmol/l)	−8·6 (1·6)	−10·1 (2·0)*

Results are means (SE) where appropriate.
The differences were not statistically significant
*Biased by one case, see text.

reduces heart rate variation in the study group may only operate *in utero*. Alternatively other factors controlling heart rate variation may have predominated 24 h after birth, temporarily obscuring a continuing difference between the groups. In sheep, there are changes in both chemo- and baro-receptor settings soon after birth, as a consequence of the alterations in blood gases and arterial pressure (Blanco *et al.* 1984, 1985), and so it is perhaps not surprising to find that heart rate and its variation alter postnatally.

FHR variation is assessed visually in terms of heart rate, whereas mean range is computed from pulse intervals. Heart rate and pulse intervals are reciprocally related, so that over a range of different basal heart rates, indices of variation derived from rate or pulse intervals are not linearly related. Thus, at higher basal heart rates, variation in terms of pulse intervals will be less than that in terms of heart rate. The basal heart rate in the study group before delivery was consistently lower than in the control group, but the differences were small and had a negligible effect on the computation of mean minute range. However, the basal heart rate fell significantly in both groups after delivery, and these considerations should be borne in mind when comparing FHR variation before and after delivery.

The clinical importance of the findings is that a few normal fetuses persistently exhibit low FHR variation which could lead to unnecessary anxiety or intervention. The results provide further evidence that the 'unreactive trace' (for example, the lower record of Fig. 3) is not a reliable indication of fetal compromise.

We now have a better evaluation of the lower limit of normality of FHR variation, estimated *over 60 min* at a mean of 31·5 (SE 1·5) ms for the lowest 3·2 centile. This compares with mean figures of 22·9 (SE 1·2) ms in fetal growth retardation or 20·6 (SE 1·2) ms in a study of 21 pregnancies associated with fetal compromise (unpublished observations).

Finally we must emphasize that the patterns considered are distinct from the decelerative or terminal traces, which do not occur normally; the latter are associated with a high risk of fetal acidaemia (Visser *et al.* 1980).

Acknowledgments

The study was supported by a grant from the Medical Research Council. We also thank Roger Belcher for help with the microproccessor system, and staff midwives Vibeke Mannion and Amanda Cartwright, who made the recordings.

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Received 29 August 1986
Accepted 26 September 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 665–669

The effect of fetal heart rate on umbilical artery flow velocity waveforms

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Summary. Umbilical artery flow velocity waveforms were obtained using continuous wave Doppler ultrasound in 85 normal pregnancies (25 antepartum, 60 intrapartum) to examine the relation between fetal heart rate, end systolic/end diastolic ratio (A/B ratio) and resistance index (RI). Our results demonstrated a significant negative correlation between fetal heart rate, A/B ratio and RI (in the antepartum group $r=-0{\cdot}49$, and in the labouring group $r=-0{\cdot}65$). It is therefore important when performing mathematical analysis of umbilical artery flow velocity profiles to make a statistical allowance for fetal heart rate.

Recent studies have reported presumed increases in placental resistance or changes in fetal circulation as reflected in alterations of flow within the umbilical artery and, therefore, in signals obtained from this vessel using Doppler ultrasound (Trudinger *et al.* 1985).

The analysis of such signals gives a characteristic waveform and its rate of deceleration and the end diastolic velocity are thought to be dependent mainly on placental resistance (Fitzgerald *et al.* 1984). All of the methods of analysis of the waveform in current use take the end diastolic velocity into account as indicative of the placental resistance (Erskine & Ritchie 1985). If the fetal heart rate slows then the value of end-diastolic velocity is likely to fall, and conversely if the fetal heart rate accelerates, the end-diastolic velocity may increase. We have been unable to find any published study on the relation between fetal heart rate and umbilical blood flow.

This paper describes a study of the relation between fetal heart rate (FHR), end systolic/end diastolic (A/B) ratio and the resistance index (RI).

Patients and methods

Doppler studies of the umbilical artery were performed in 85 uncomplicated pregnancies between 38 and 42 weeks of gestation. All pregnancies had the gestation confirmed by ultrasound in early pregnancy. Twenty-five women (the antenatal group) were studied during pregnancy on a total of 34 occasions. An average of five frames each containing three cardiac cycles were recorded for study on each occasion.

Sixty women were studied during labour (labour group). Each patient was studied immediately after amniotomy and every 2 h thereafter until delivery. Six frames of three cardiac cycles were recorded on each occasion.

In all women, labour occurred spontaneously after 37 completed weeks gestation. All infants were in good condition with Apgar scores of >7 at 1 min and >9 at 5 min, and with birthweights >10th centile for gestational age after correction for maternal height and weight (Altman & Coles 1980).

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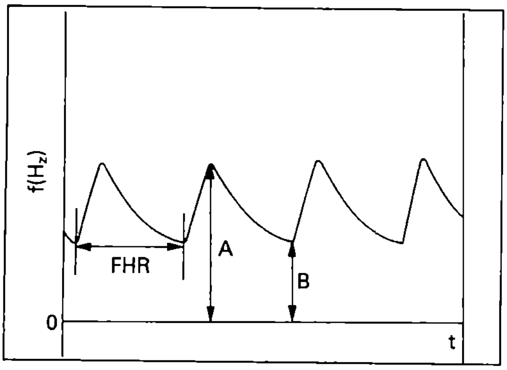

Fig. 1. Characteristic umbilical artery flow velocity waveform. A, Peak systolic frequency; B, end diastolic frequency; FHR, fetal heart rates; RI $\frac{A-B}{A}$

Measurements

The Doppler signals from the umbilical artery were obtained using a 4 MHz Sonicaid continuous wave ultrasound probe with the women lying comfortably in a semi-recumbent position. The probe was placed on the abdomen and positioned to obtain the best quality signals from the umbilical artery recognized by its characteristic sound with the low frequency signal from the umbilical vein in the opposite direction. Readings were not taken during fetal breathing or gross body movements. In the labouring patients measurements were taken between contractions.

Spectral analyses were performed on these signals using a Unigon Angioscan III with a 300 Hz high pass filter. The waveform patterns were stored on discs using an Apple IIe computer, and a permanent record obtained from an on-line Canon colour printer.

The ratio of peak systolic frequency (A) to least diastolic frequency (B) was measured, and A/B ratio and resistance index (RI) were calculated (Fig. 1). The use of the A/B ratio or RI eliminates the need to know the angle of insonation of the artery. The fetal heart rate was obtained by calculating the time taken to complete one cardiac cycle.

Results

In each group there was a significant negative correlation between fetal heart rate, and both A/B ratio and RI.

Antenatal group

A total of 169 recordings were taken in this group on 34 occasions in 25 women (Fig. 2). For each value of FHR, the mean A/B ratio and RI were plotted with the range. The degree of negative correlation between FHR, A/B ratio and RI was significant. For A/B ratio: $r=-0{\cdot}49$, $P<0{\cdot}02$, $y=4{\cdot}32-0{\cdot}014x$ and for RI: $r=-0{\cdot}49$, $P<0{\cdot}02$, $y=0{\cdot}93-2{\cdot}66\times10^{-3}x$, the correlation and regression coefficients and P value were calculated on a subset of the data obtained taking a random sample of one observation from each subject.

The inverse relation between FHR, A/B ratio and RI holds within individual pregnancies. The FHR is not constant, and can alter quite considerably even during a short period of recording. In one woman the recordings taken at a single antenatal visit of 38 weeks gestation showed an FHR variation from 117 to 162 beats/min, with corresponding A/B ratios of 2·8 and 2·00, and RI of 0·64 and 0·5 ($r=-0{\cdot}93$, $P<0{\cdot}01$ for both A/B ratio and RI, Fig. 3).

Labour group

A total of 1137 recordings were obtained in the 60 women studied during labour (Fig. 4). The degree of negative correlation was highly significant. For A/B ratio: $r=-0{\cdot}65$, $P<0{\cdot}001$, $y=4{\cdot}24-0{\cdot}015x$ and for RI: $r=-0{\cdot}65$, $P<0{\cdot}001$, $y=0{\cdot}88-2{\cdot}67\times10^{-3}x$, the correlation and

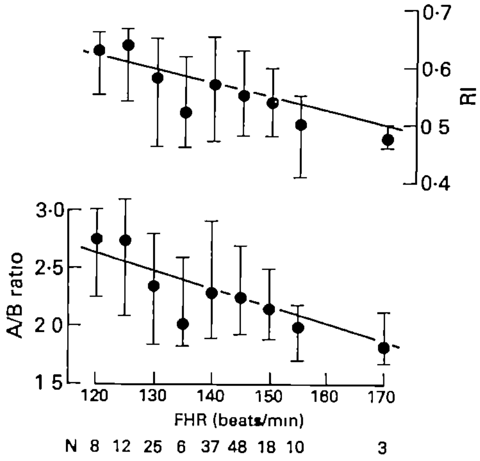

Fig. 2. Effect of FHR on A/B ratio and RI based on 169 observations in 25 women during pregnancy. N, Number of observations made at each FHR; the vertical bars show the mean and range.

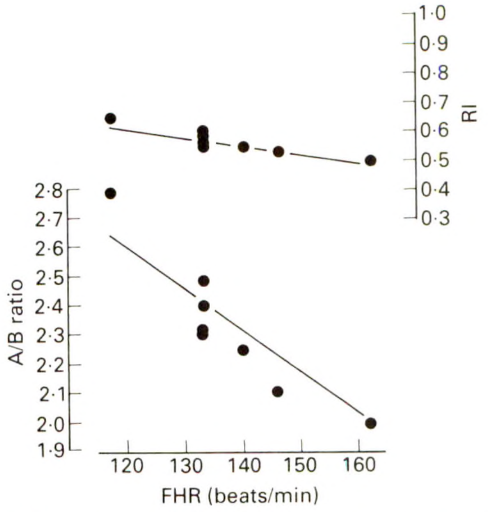

Fig. 3. Effects of FHR on A/B ratio and RI based on eight observations taken at a single session in a normal pregnancy at 38 weeks of gestation.

regression coefficients and *P* value were calculated from a similar subset of data as in the antenatal group. Although the range of FHR was 90 to 175 beats/min which is greater than that obtained in the antenatal group, most recordings were again taken between FHR 130 to 145. Between these extremes of FHR (90–175) the A/B ratio changed from 3·4 to 1·7 and the RI from 0·71 to 0·41. As in the antenatal group, the inverse relation between FHR, A/B ratio and RI still held in individual cases. It was possible, therefore, to calculate very different A/B ratios and RI within the same pregnancy depending on the FHR at the time of recording. The range of A/B ratio and RI at the lower FHR of 90 and 100 beats/min was much greater than that obtained for FHR above 120 beats/min.

Discussion

Previous studies have reported that changes in umbilical artery flow velocity waveforms, obtained using Doppler ultrasound, are related to fetal outcome in high-risk pregnancies (Trudinger *et al.* 1985; Erskine & Ritchie 1985). These studies have suggested that fetal compromise is associated with a high A/B ratio which has been interpreted as reflecting a high resistance placenta. Assuming no short-term variation in placental resistance in these apparently normal pregnancies, we have found an inverse relation between FHR and both A/B ratio and RI. The umbilical artery flow velocity waveform patterns from the patient described in Fig. 3 is illustrated to show why FHR has an effect on A/B ratio and RI (Fig. 5). Examination of these waveform patterns shows that at slower FHR a lower end diastolic frequency is obtained before the next cardiac impulse travels down the vessel. This gives a corresponding increase in A/B ratio and RI. Likewise at faster FHR a higher end diastolic frequency is obtained, as the cardiac impulses are occurring more frequently, and a lower A/B ratio and RI are obtained. At the slower FHR of 90–100 found in the labouring patients, the range of A/B ratios and RIs above the mean was clearly greater than could have been expected by FHR and we suspect that umbilical cord compression causing increased resistance may be a contributing factor.

In individual pregnancies the FHR is not constant. It is known that there is a natural circadian rhythm and that heart rate changes in association with fetal movements, fetal breathing movements, maternal heart rate and uterine activity (Patrick *et al.* 1982; Sadovsky *et al.* 1983). We have found that even during a short period of recording the FHR alters quite considerably and this is reflected in the results obtained. Indeed it may be that in some cases of

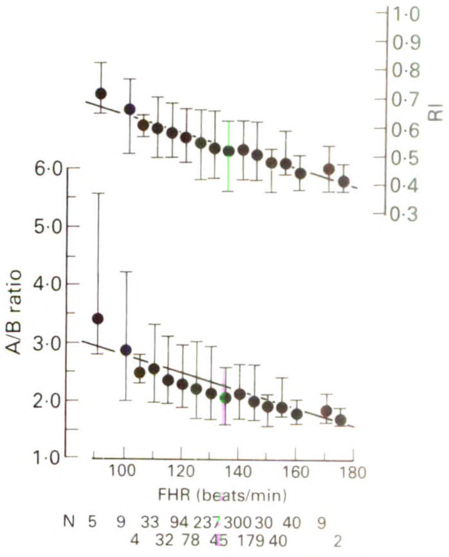

Fig. 4. Effect of FHR on A/B ratio and RI based on 1137 observations made on 60 women in labour. N, Number of observations made at each FHR; the vertical bars show the mean and range.

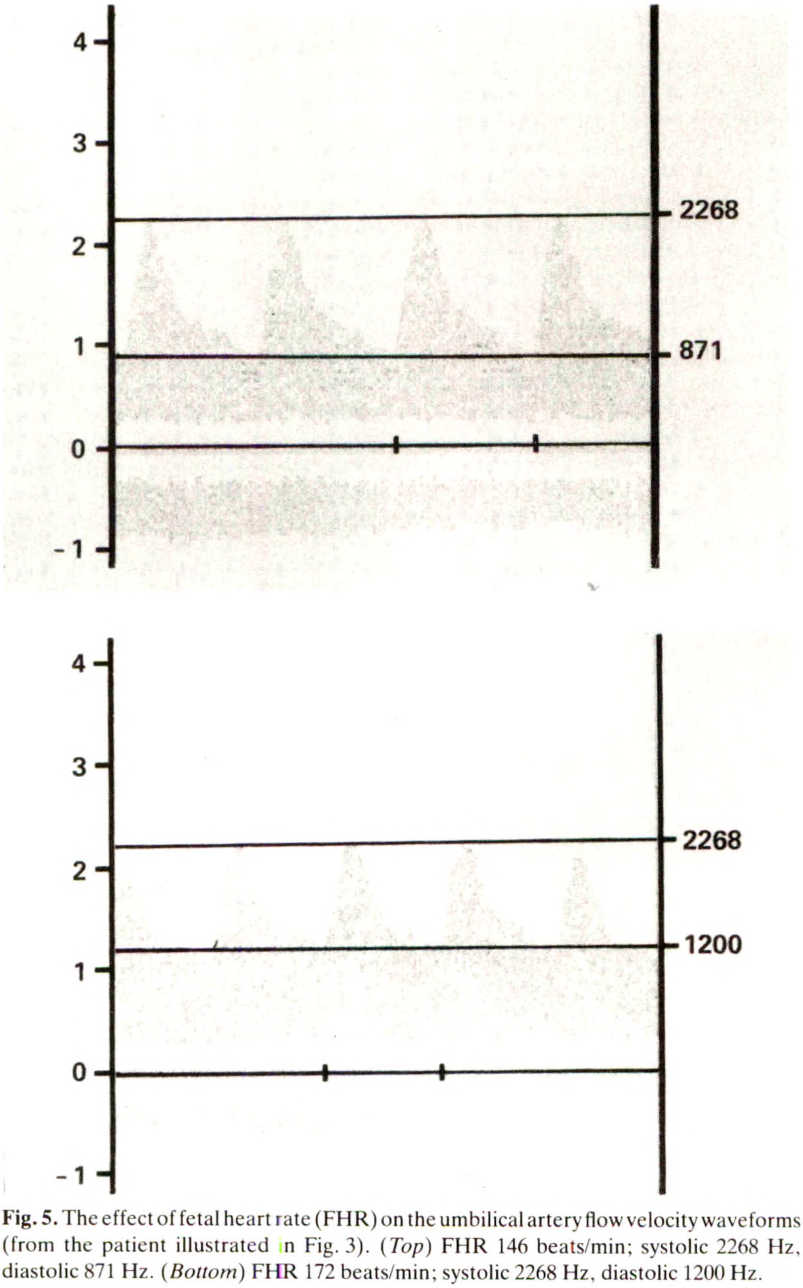

Fig. 5. The effect of fetal heart rate (FHR) on the umbilical artery flow velocity waveforms (from the patient illustrated in Fig. 3). (*Top*) FHR 146 beats/min; systolic 2268 Hz, diastolic 871 Hz. (*Bottom*) FHR 172 beats/min; systolic 2268 Hz, diastolic 1200 Hz.

high values of A/B ratio and RI that these ratios are merely reflecting deceleration in the FHR and not resistance changes at all. The modal FHR in the study was 140 beats/min. To minimize the effect of FHR on A/B ratio and RI it is possible to standardize these ratios for 140 beats/min using the regression equations described in this study, e.g. for antenatal patients corrected A/B ratio=observed A/B ratio$-0{\cdot}014\times(140-$observed FHR).

Further studies are currently being undertaken to investigate earlier gestations and compromised fetuses to determine whether a similar inverse relation between FHR, A/B ratio and RI exists in these situations.

Acknowledgments

We gratefully acknowledge Mr S. Ogston for the statistical advice and Miss Beverly Reid for typing the manuscript. This work was supported by the Cunningham Trust.

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Received 15 July 1986
Accepted 6 March 1987

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 670–674

Mortality and morbidity in infants born between 20 and 28 weeks gestation

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Summary. Of 149 infants with ultrasound evidence of gestational age, born in Ninewells Hospital at between 20 and 28 weeks gestation over a 5-year period, 50 were alive at birth. Of these infants, 21 died within 1 week, a further three died within 1 month and a further two within 18 months. Of the 24 survivors, 8 (33%) have significant handicap. The obstetric factors leading to delivery and the mode of delivery are discussed.

Several studies have described survival rates in very-low-birthweight infants (<1500 g) and extremely-low-birthweight infants (<1000 g) (Stewart *et al.* 1981; Yu *et al.* 1981; Kitchen *et al.* 1982) and have quoted the survival statistics in relation to birthweight. Whereas the neonatologist may be sure of the birthweight, the index by which obstetricians manage very preterm delivery is gestational age. We have found four studies of which have used gestational age as a framework for the analysis and presentation of mortality and morbidity (Dillon & Egan 1981; Philip *et al.* 1981; Herschel *et al.* 1982; Yu *et al.* 1984). In these studies gestational age was assessed on the basis of last menstrual period (with allowances made for differing cycle lengths), or clinical estimation of uterine size, or when fetal movements were first felt or by ultrasound scans where these were available. The frequency of ultrasound scanning to estimate gestation was not stated in these studies, except in the one by Dillon & Egan (1981) where 32 of 57 women (56%) had had a mid-trimester ultrasound scan.

All women in Dundee are delivered in Ninewells Hospital and most have an ultrasound scan at 19 weeks for confirmation of gestational age and to exclude multiple pregnancy or fetal abnormality. Ultrasound is readily available and liberally used earlier in pregnancy if there have been problems, and as a consequence, most of our patients have had at least one scan before 20 weeks gestation. This study reports the outcome of all pregnancies in a single population ending between 20 and 28 weeks gestation over a 5-year period

Patients and methods

The details of all pregnancies ending between 20 and 28 weeks in our hospital are recorded on a 'late abortion' file.

Therapeutic terminations of pregnancy for fetal abnormality or social reasons were excluded from this study. Between 1 January, 1980 and 31 December, 1984, 156 infants were born at between 20 and 28 weeks gestation (12 sets of twins) Of the 144 mothers, 137 had had an ultrasound scan before 20 weeks gestation, the other seven women were excluded from the study (five of them had not had a scan requested, and two were unbooked). The case records of the remaining 149 infants were reviewed. The total number of stillbirths and live infants born after 28 weeks gestation during the 5-year study period was 17 371.

Preterm infants with birthweights of ≤1500 g are followed up at a neuro-developmental assessment clinic and information on each surviving infant's subsequent progress was

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recorded for a minimum of 18 months following delivery. The developmental schedules are based on those of Gesell (Knobloch & Passamanick 1974; Knobloch *et al.* 1980).

For the purposes of defining mode of delivery, where a lower segment transverse incision was extended to form an inverted T this was recorded as a classical caesarean section.

In an attempt to determine the causes of these very premature deliveries, the principal precipitating factors leading to delivery were noted. Inevitably there was some overlap as some pregnancies had several adverse factors. Wherever possible the first identified underlying pathology was used to categorize the causes of fetal loss. Thus if preterm spontaneous rupture of membranes was followed by infection then intrauterine death, the precipitating factor was categorized as spontaneous rupture of membranes.

Results

Of the 149 infants studied, 99 were registered as abortions. Of the 50 infants who were live born, 21 died within 1 week, three died within 1 month and a further two within 18 months. Of the 24 still surviving, eight have a major degree of physical or mental handiap although in one case the handicap is congenital in origin.

Table 1 shows the precipitating cause for the delivery and the subsequent outcome. The most frequent cause of delivery was spontaneous premature labour ($n = 71$, 48%). Except for the 11 patients who were admitted in advanced labour with a cervical dilatation of >5 cm and the 20 patients at less than 24 weeks gestation, ritodrine was used intravenously at maximum tolerated dosage in an attempt to stop labour without success. Other common precipitating factors were antepartum haemorrhage ($n = 23$, 15%) and preterm rupture of the membranes ($n = 21$, 14%).

Table 2 shows the mortality and morbidity in twins and in singleton infants. Twins represented 16% of this study group. The precipitating causes of delivery in the 12 twin pregnancies were spontaneous premature labour in 10, spontaneous preterm rupture of the membranes in one and severe proteinuric pre-eclampsia in the last, which was delivered by caesarean section. Only 11 of the 24 twin infants (46%) were stillbirths compared with 88 of the 125 singleton infants (70%). Of the 10 twin infants who survived >28 days, six (60%) are still alive without handicap compared with 10 (63%) of the 16 singleton infants who survived >28 days.

Table 3 shows the mortality and morbidity of the live born infants by gestation at delivery. Only one infant born at less than 26 weeks gestation survived during the 5-year study and to date shows no signs of handicap. Of the 41 live born infants of 26 weeks gestation or more, 18 died, eight survived with significant handicap, and 15 survived with no handicap. In only one infant is the handicap known to be congenital in origin (osteogenesis imperfecta).

Table 4 describes outcome by mode of delivery. Although numbers are small it is of note that there were no healthy survivors born by classical caesarean section. Five of the 15 vaginal breech births are still alive with no handicap detected.

Discussion

Ours is the only series that we know which is population based and where all pregnancies had an ultrasound scan before 20 weeks gestation to determine gestational age. In the study by Philip *et al.* (1981) many infants had been transferred for intensive neonatal care after they were born in other units, introducing factors such as differing referral rates and absence of a denominator of total live births which makes interpretation of mortality and morbidity rates difficult. The study by Herschel *et al.* (1982) only described neonatal survival rates thereby taking no account of the increasing number of post-neonatal deaths as paediatricians manage to help very small infants survive beyond the statutory 28 days.

In our population the incidence of ultrasound scanning before 20 weeks gestation was very high during the 5 years reviewed (95·5%), and accurate knowledge of gestational age is bound to have influenced the obstetric and paediatric management. Results from other centres with less certain knowledge of gestational age may well be different. A rather surprising finding of this retrospective review was the low number of fetuses recorded as live births at <26 weeks gestation. One of the problems of a retrospective review such as this is that one can only rely on what the attendants at the birth have recorded in the notes about whether these infants showed any signs of life. Although all fetuses that show any signs of life should be

Table 1. Precipitating factors in delivery between 20 and 28 weeks gestation and outcome

	Outcome							
		Live born but died						
Cause	Stillborn/ abortion	<7 days	8–28 days	1–18 months	Alive/ handicapped	Alive/ well	Total	(%)
Premature labour	39	14	3	2	5*	8	71	(47·7)
Antepartum haemorrhage	15	5				3	23	(15·4)
Spontaneous membrane rupture	15	1			3†	2	21	(14·1)
Unexplained fetal death	7						7	(4·7)
Fetal growth retardation	2						2	(1·3)
Fetal hypoxia	1						1	(0·7)
Fetal abnormality	3						3	(2·0)
Hypertension	4					3	7	(4·7)
Cervical incompetence	5	1					6	(4·0)
Maternal disease	1						1	(0·7)
Infection	7						7	(4·7)
Total no. (%)	99 (66·4)	21 (10·1)	3 (2·0)	2 (1·3)	8 (5·4)	16 (10·7)		

Type of handicap * right hemiplegia, right hemiplegia, blind, blind, osteogenesis imperfecta; † left hemiplegia, microcephaly, spastic diplegia.

Table 2. Survival, death and handicap in singleton and twin infants born between 20 and 28 weeks gestation

		Deaths			Alive		
	Abortion	<7 days	7–28 days	1–18 months	Handicapped	Well	Total
Singleton	88	20	1		6	10	125
Twin	11	1	2	2	2	6	24

registered as a live birth even if they give only one gasp, there is a tendency in this country for attendants to register such a fetus as showing no signs of life (and therefore an abortion) because of the legal and emotional implications for the parents. If classified as live born and the infant then dies, the parents must register the birth and death and decide funeral arrangements, despite the fact that the fetus may have been too immature for any resuscitation. We suspect that the low number of live births, less than 26 weeks gestation, recorded by labour ward attendants, may reflect this. Indeed, in a population such as this where the gestational age is well documented this factor may be much more in evidence.

Although twin pregnancies contributed significantly to cases in this study, the infants did well in the long term; 25% survived without handicap. However, these crude figures give a falsely low incidence of healthy survival for singletons, since there were many more singletons dead at birth (88 of 125). The mean gestational age at delivery for live born singletons was 25·6 weeks and 26·8 weeks for live born twins, and this may explain the larger number of twins surviving. Of the infants who survived the first month of life, the percentage who survived without handicap was 62% in singletons and 60% in twins.

Of the three classical caesarean sections (four infants; one set of twins) only one infant survived but was severely handicapped. Of the 12 born by lower segment caesarean sections, six still survive although only four are without handicap. Few conclusions can be drawn from this, since classical caesarean sections were used where a difficult birth was expected or encountered during an attempt at lower segment caesarean section (one spontaneous rupture of membranes in labour with transverse lie, one set of twins at 26 weeks, one failed lower segment

Table 3. Mortality and morbidity of live born infants delivered between 20 and 28 weeks gestation

Gestation (weeks)	Mean birthweight (g)	Dead	Alive and well	Alive with handicap	Type of handicap
<26	681	8	1	—	—
26–27	889	7	4	1	Right hemiparesis squint but intellect normal
28	978	11	11	7	(1) Right hemiparesis and retarded; (2) osteogenesis imperfecta; (3) spastic diplegia; (4) left hemiparesis and epilepsy; (5) microcephaly, (6) and (7) blindness, retrolental fibroplasia

Table 4. The mortality and morbidity of infants born between 20 and 28 weeks gestation by mode of delivery

Mode of delivery	Abortion	Deaths <7 days	Deaths 7–28 days	Deaths 1 month–2 years	Survived handicapped	Alive and well
CCS	1*	2	—	—	1*	—
LSCS	—	3	2	1	2	4
Forceps	7	3	—	—	1	2
Vaginal breech	10	6	1	—	3	5
SVD	81	7	—	1	1	5
Total	99	21	3	2	8	16

* Twins.
SVD, Spontaneous vaginal delivery.
CCS, Classical caesarean section.
LSCS, Lower segment caesarean section.

caesarean section extended to a T incision). Of the 15 vaginal breech livebirths, five infants are still surviving with no handicap.

Although in our study by far the commonest outcome of birth between 20 and 28 weeks gestation was death, two-thirds were stillbirths and 83% were dead by 1 month, survival without handicap occurred in 11%. Some improvements in this picture will no doubt come from strategies available at present, i.e. prevention of hypoxaemia and trauma during delivery and intensive neonatal care, but more significant improvements would be achieved if preterm births could be prevented. The most frequent precipitating factors including spontaneous onset of labour, spontaneous rupture of membranes and multiple pregnancy, affected potentially normal infants. Whilst research continues into the causes of premature labour and spontaneous rupture of membranes, one group at high risk of mid-trimester miscarriage that can be detected early are multiple pregnancies. This gives support to the widespread use of ultrasound scans in early pregnancy. Since obstetricians have to manage pregnancies on the basis of gestational age, and since the occurrence of problems in mid-trimester can seldom be predicted, confirmation of gestational age early in all pregnancies is important.

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Received 12 June 1986
Accepted 19 September 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol 94, pp 675–677

Amniotic fluid and fetal tissues are not heated by obstetric ultrasound scanning

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Summary. Amniotic fluid temperature in first trimester pregnancies and fetal subcutaneous tissue and amniotic fluid temperature in second trimester pregnancies, measured by a thermocouple probe, did not increase during sector, linear-array or Doppler ultrasound scanning. The mean fetal muscle temperature was higher (36·9°C) than mean amniotic fluid temperature (36·6°C) during the second trimester.

An assertion such as 'ultrasound is safe' cannot be proven (Popper 1959). Attempts must continue to disprove it, particularly as in the UK 70–80% of human fetuses are exposed to ultrasound (Report of the RCOG Working Party 1984). Animal studies have shown that ultrasound can have biological effects and that fetal abnormalities and growth retardation are more common after exposure to high doses of ultrasound (Takabayashi *et al.* 1981; O'Brien 1983). Recognized mechanisms by which ultrasound could produce these effects include heating and mechanical damage. Reported experiments in small animals support the view that heating by 2·5–5°C was likely to have occurred when abnormalities were produced (Report of the RCOG Working Party 1984; Lele 1975).

Calculations predict that the low intensity, pulsed ultrasound used in obstetric scanning would produce little heating (Nyborg & Steele 1983). However, these are based on assumptions about the attenuation and absorption of the beam energy in different tissues and the diffusion of heat away from the insonated area either directly through tissues or in blood; no direct measurements of temperature change during obstetric scanning have been reported.

We therefore measured intrauterine temperature during three types of obstetric scanning.

Patients and methods

The pregnancies of 30 women undergoing elective first or second trimester abortions (8–20 weeks gestation) who gave informed consent were studied.

A brain temperature probe (A.W. Staniforth Ltd., London) was specially modified for this study. A thermocouple at the tip of a 28 cm, 20 gauge needle was used with an electrical thermometer with a digital display (Type DU 81 Elab, Copenhagen). This equipment was checked before and after the insonation experiments in a water bath with a fertility thermometer (Zeal, London) over the range 35–39°C and agreement to 0·1°C was found. It equilibrated within 2 s, and warming the shaft did not affect the temperature reading.

First trimester scanning

Series 1: Sector scanning. In 10 patients under general anaesthesia for suction termination of pregnancy, an 18 gauge guide cannula (as used for a chorionic villus biopsy) with a stilette was introduced transcervically into the amniotic cavity. The stilette was removed, the temperature probe was passed into the amniotic sac and the cannula withdrawn. After 1 min for equilibration the temperature was recorded. With a sector ultrasound scanner [ADR 4000, 17 mm, 3

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MHz; spatial-peak temporal average (SPTA) intensity 3 mW/cm^2; where SPTA is the maximum value of intensity occurring in the beam averaged over the pulse repetition period] the tip of the probe was identified and insonated for 3 min. The temperature was measured continuously and recorded at 1-min intervals before, during and for 2 min after cessation of scanning. Suction termination of pregnancy was then performed uneventfully.

Second trimester scanning

Before intra-amniotic injection of prostaglandins for elective abortion in 20 pregnancies at 16–20 weeks gestation, the temperature probe was passed down a 19 gauge needle into the amniotic cavity under materno-fetal sedation (papaveretum 20 mg i.m) and maternal local anaesthesia. After completion of the study prostaglandin termination was performed uneventfully in all patients.

Series 2: Linear-array scanning. In 10 patients the probe tip was identified in the amniotic cavity and insonated for 3 min, with a linear-array scanner (Hitachi EUB 26, 3 MHz; SPTA 1·1 mW/cm^2). The temperature was recorded as in series 1.

Series 3: Doppler scanning. In 10 further patients, the thermocouple tip was directed into fetal subcutaneous tissue and identified with the linear-array transducer of the Kranzbuhler 8130 machine. The pulsed, Doppler beam (SPTA 112 mW/cm^2) was directed onto the tip for 10 min. Temperature was measured continuously and recorded at 1-min intervals before and during insonation (in this series, readings were not taken after cessation of scanning).

Statistical analysis

The comparison of the temperatures before scanning was made using Student's *t*-test of two means. The paired *t*-test was used to compare the temperatures before with those after scanning

Results

The mean amniotic fluid temperature did not differ significantly between first and second trimester pregnancies; the respective values were 36·7 (SE 0·12)°C and 36·6 (SE 0·12)°C. The mean fetal subcutaneous temperature in the second trimester pregnancies was 36·9 (SE 0·04)°C which was significantly higher than that of the amniotic fluid (mean 36·6, SE 0·12°C) ($t = 2{\cdot}3$, $P < 0{\cdot}05$).

The results in Table 1 show that there were no significant changes in amniotic fluid temperature with sector scanning (series 1, paired $t = 0{\cdot}08$) or linear-array scanning (series 2, paired $t = 0{\cdot}3$), or in fetal tissue temperature during Doppler ultrasound scanning (series 3, paired $t = 0{\cdot}06$). The individual data from series 3 are shown in the figure as this group was exposed both to the highest intensity of ultrasound and for the longest period of time.

Discussion

These are the first reported measurements of human fetal and amniotic fluid temperature

Table 1. The effect of ultrasound on fetal and amniotic fluid temperature

Series	Temperature in relation to insonation (°C)		
	Before	During*	After*
1. Amniotic fluid temperature during first trimester sector scanning ($n = 10$)	36·7 (0·12)	36·6 (0·12)	36·6 (0 13)
2. Amniotic fluid temperature during second trimester linear-array scanning ($n = 10$)	36·6 (0 12)	36·6 (0 13)	36·6 (0·12)
3. Fetal tissue temperature during second trimester Doppler scanning ($n = 10$)	36·9 (0·04)	36 9 (0·02)	

*Series 1 and 2 were insonated for 3 min and Series 3 for 10 min; the 'after' temperature was recorded 2 min after stopping insonation.

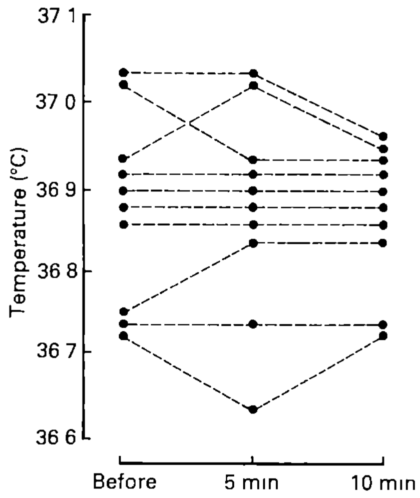

Fig. 1. Subcutaneous tissue temperature before and after 5 and 10 min of Doppler scanning in 10 fetuses (series 3). Paired $t_{0\text{-}10\ \mathrm{min}} = 0{\cdot}06$ (NS).

before labour or membrane rupture. The temperature gradient from fetus (36·9°C) to amniotic fluid (36·6°C) indicates that, like other animals (Hart & Faber 1965), the human fetus may lose a substantial proportion of the heat produced by its metabolism to the amniotic fluid. A similar gradient, but at a higher temperature, between human fetal rectum (37·6°C) and amniotic fluid (37·2°C) was detected during early labour in fetuses presenting by the breech (Wood & Beard 1964). These higher temperatures may have been due to increased fetal heat production in response to the onset of labour or because of the later gestational age studied (37–40 weeks).

Our failure to detect any heating of amniotic fluid by sector or linear-array scanning or of fetal subcutaneous tissue by Doppler scanning, using equipment capable of measuring to an accuracy of 0·1°C, is reassuring since this is much less than the 2°C increase shown to damage other animal fetuses (Report of the RCOG Working Party 1984). The Doppler scanner has an SPTA of 112 mW/cm^2 which is higher than a recommended (AIUM Bioeffects Committee 1983) maximum of 100 mW/cm^2 but even this intensity did not produce heating when directed at one part of the fetus for 10 min. Furthermore, in a ultrasound examination, the transducer is moved about and is not pointed at one area for long.

These results suggest that intrauterine heating does not occur during diagnostic obstetric ultrasound scanning and that this cannot therefore be a mechanism of fetal damage.

Acknowledgments

We are grateful to Dr Mary Dyson for helpful discussion and Dr Francis Duck for measuring the SPTA of the ultrasound machines used.

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Received 3 July 1986
Accepted 10 August 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 678–681

Cigarette consumption and serum cotinine in relation to birthweight

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Summary. The concentration of serum cotinine (the major metabolite of nicotine) was measured in sera from 4211 women at between 15 and 21 weeks gestation to determine whether a serum cotinine level was a better predictor of low birthweight than the self-reported number of cigarettes smoked per day. Both cotinine levels and smoking history were significantly associated with reduced birthweight, but cotinine correlated significantly better. Smokers of ≥25 cigarettes per day, representing the 2·7% of women with the greatest cigarette consumption, had infants 289 g lighter than the 68% of women who were non-smokers. Women with serum cotinine levels in the top 2·7% (≥284 ng/ml) had infants 441 g lighter than the 68% of women with the lowest cotinine levels (≤24 ng/ml). Our results strengthen the evidence linking smoking with low birthweight and also demonstrate that cotinine can be satisfactorily used to assess and monitor cigarette smoking in pregnancy.

Studies on smoking and health have been based generally on the reported number of cigarettes smoked daily (Kannel 1981) Some of these studies have also taken into account the manner of smoking and composition of cigarette smoke (Kaufman *et al.* 1983; Borland *et al.* 1983). Only a few studies compared quantitative biochemical measurements of various cigarette smoke products in blood, such as carboxyhaemoglobin or thiocyanate, with cigarette numbers in relation either to existing (Wald *et al.* 1973; Heliovaara *et al* 1981) or future (Heliovaara *et al.* 1981) health problems. We had access to a large number of antenatal serum samples as part of an alpha-fetoprotein (AFP) screening programme for open neural tube defects (Haddow *et al.* 1983) together with information on smoking and a reliable assay, and this prompted us to investigate whether serum cotinine would be a better predictor of reduced birthweight than the reported number of cigarettes smoked each day

Subjects and methods

On the serum AFP request form, information is routinely sought on whether the woman concerned smokes cigarettes and, if so, how many cigarettes each day. Our analysis was based on women screened between July 1980 and June 1983, and was restricted to the 4211 women who provided an adequate blood sample between 15 and 21 weeks gestation (representing 97% of women screened), were known to have singleton, liveborn babies without neural tube

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Table 1. Serum cotinine levels according to cigarette consumption

	Number of women	Serum cotinine (ng/ml) centile		
		10th	50th	90th
Non-smokers	2871	≤10	≤10	≤10
Smokers (cigarettes/day)				
1–7	247	≤10	68	177
8–12	410	36	119	248
13–17	96	59	135	289
18–24	472	54	159	292
≥25	115	84	184	303
All smokers	1340	31	134	272

Table 2. Number of women, mean birthweight (BWT) and percentage of birthweights ≤2800 g according to reported number of cigarettes smoked each day and serum cotinine

Serum cotinine (ng/ml) Category (mean)		Number of cigarettes/day						
		0 (0)	1–7 (4·2)	8–12 (9·9)	13–17 (15·0)	18–24 (20·0)	≥25 (34 1)	All
	No women	2759	62	32	4	15	2	2874
0–24	Mean BWT	3508	3475	3633	3548	3598	3231	3509
(1)	Percent ≤2800 g	7·5	6·5	3·1	0	0	0	7·4
	No women	44	62	71	9	51	8	245
25–69	Mean BWT	3329	3358	3419	3511	3286	3345	3360
(48)	Percent ≤2800 g	11 4	14·5	8·5	0	15·7	0	11·4
	No. women	35	73	126	37	117	20	408
70–137	Mean BWT	3429	3367	3430	3262	3313	3507	3373
(103)	Percent ≤2800 g	17·1	8·2	7·1	10·8	11·1	10·0	9·8
	No. women	8	14	26	6	41	5	100
138–153	Mean BWT	3625	3472	3232	3044	3260	3455	3293
(145)	Percent ≤2800 g	0	7 1	11·5	50·0	26·8	0	18·0
	No. women	20	30	132	30	194	64	470
154–284	Mean BWT	3277	3225	3131	3136	3195	3154	3173
(209)	Percent ≤2800 g	15·0	20·0	22·0	30·0	14·9	20·3	18·9
	No. women	5	6	23	10	54	16	114
>284	Mean BWT	3594	3230	3083	2890	3065	2943	3068
(350)	Percent ≤2800 g	0·0	33·3	17·4	60·0	27·8	31·3	28·1
	No. women	2871	247	410	96	472	115	4211
All	Mean BWT	3503	3376	3316	3206	3235	3214	3433
	Percent ≤2800 g	7 7	11·3	12·7	22·9	16·0	17·4	10·0

defects, and had provided information on smoking. Serum cotinine was measured by radioimmunoassay (Knight *et al.* 1985). The lower limit of assay sensitivity was 10 ng/ml and values ≤10 ng/ml were recorded as such.

Results

Table 1 shows serum cotinine levels according to cigarette consumption. There is a steady increase in the median serum cotinine level with increasing cigarette consumption, albeit with considerable overlap between smoking categories. For example, of women who smoked 1–4 cigarettes/day, 30% had serum continine levels above 100 ng/ml. By contrast, among women smoking at least 20 cigarettes/day, 13% had serum cotinine levels below 100 ng/ml.

Table 2 shows the mean birthweight and percentage of birthweights of ≤2800 g, according to cigarette consumption and serum cotinine level. In this table, the smoking categories other than non-smokers were defined such that the mean value of the interval fell approximately on the number of cigarettes most commonly reported, usually either 5, 10, 15, 20, etc, cigarettes per day. Cotinine categories were then chosen so as to match the numbers in each smoking category as closely as possible, so that, for example, 68% of women said they were non-smokers and 68% of women were in the lowest cotinine category (0–24 ng/ml). Birthweights of ≤2800 g were used to define our low birthweight category instead of the more conventional ≤2500 g to avoid obtaining too few numbers in the cells of the table. Univariate linear regressions showed that cigarette consumption and serum cotinine were both inversely associated with birthweight ($r = -0{\cdot}19$, $P<0{\cdot}001$ and $r = -0{\cdot}23$, $P<0{\cdot}001$ respectively). It is evident from Table 2, however, that the mean birthweight decreases more in relation to increases in serum cotinine level (arranged vertically) than according to increases in reported cigarette consumption (arranged horizontally). Smokers of ≥25 cigarettes per day (115 women, 2·7%) had infants 289 g lighter than non-smokers, while women with cotinine levels of ≥284 ng/ml (114 women, 2·7%) had infants that were 441 g lighter. Similarly, the proportion of women who had infants weighing ≤2800 g tended to increase more in relation to serum cotinine level than according to reported number of cigarettes smoked each day. To determine whether serum cotinine or the reported number of cigarettes smoked per day was the better predictor of birthweight we used Healy's modification of Hotelling's method (Healy 1955). This analysis showed that serum cotinine was a significantly better predictor ($P<0{\cdot}0005$, $t = 4{\cdot}2$).

Discussion

There are very few studies of biochemical markers of tobacco smoke intake in relation to disease end-points. In two studies (Wald *et al.* 1973; Heliovaara *et al.* 1978), carboxyhaemoglobin measurements were found to be more strongly associated with existing atherosclerotic disease than cigarette consumption, although in one of the two studies the additional contribution of the biochemical marker was of limited value. In a prospective study of total mortality and mortality from coronary heart disease and lung cancer (Heliovaara *et al.* 1978), serum thiocyanate levels were of uncertain additional value, showing significant independent effects in some analyses but not in others. Cotinine is probably the best biochemical marker of exposure to tobacco smoke (Knight *et al.* 1985; Benowitz *et al.* 1983). As the major metabolite of nicotine, it is specific for tobacco and, thereby, has advantages over less specific markers such as carboxyhaemoglobin or thiocyanate. Further, cotinine's half-life of about 20–24 h in the circulation (Benowitz *et al.* 1983) provides a representative measure of cigarette smoke absorbed over the preceding few days.

Previous studies of biochemical markers of tobacco smoke intake in pregnancy have not examined whether such measurements predict adverse outcomes (such as low birthweight) better than cigarette consumption alone (Sexton & Hebel 1984; Bottoms *et al.* 1982; Jensen & Foss 1981; van Vunakis *et al.* 1974). Our study has demonstrated that this is the case with serum cotinine. Women with cotinine levels above 150 ng/ml (14% of our pregnancy population) had 2·6 times the risk of having an infant with a birthweight of ≤2800 g compared to all the women in our study. In our analysis, we did not consider other variables associated with low birthweight such as parity or maternal weight, since we wished only to compare two measures of smoking (cigarette consumption and serum cotinine) to see which was the better predictor of low birthweight. Our results strengthen the evidence linking smoking with low birthweight and also demonstrate that continine can be satisfactorily used to assess and monitor cigarette smoking in pregnancy.

Acknowledgments

We thank Argilla George and Jon Haddow for performing the cotinine measurements; Maxine Brady and Wilfred Turgeon for collecting and organizing the pregnancy outcome data; Simon Thompson for statistical advice, and Joanne Beaudoin for the manuscript preparation.

The project on which this publication is based was performed, in part, with funding from the Division of Child Health, Bureau of Health, Maine Department of Human Services and NICHD Grant no. 1-RO1-HD-18274-01.

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Received 6 June 1986
Accepted 15 October 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 682–686

Endocrine changes following pituitary desensitization with LHRH agonist and administration of purified FSH to induce follicular maturation

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Summary. Pituitary desensitization was induced in 13 normally menstruating women by administration of an LHRH agonist, Buserelin, intranasally, 100 μg at intervals of 4 h, for a period of 14 days starting on day 22 of the menstrual cycle. Whilst continuing with Buserelin, multiple follicular development was induced by administration of purified FSH (Metrodin) for between 8 and 15 days at a dose of 150 i.u. daily. In one patient no follicular growth was induced after 14 days treatment. In the remaining subjects between 3 and 11 follicles with mean diameter >16 mm were stimulated and between 2 and 10 mature oocytes were recovered laparoscopically for IVF, 34 h after hCG administration. Eight patients underwent embryo transfer and four conceived.

One factor in achieving successful pregnancy after in-vitro fertilization (IVF) is the replacement of more than one embryo. Most ovulation-induction regimens currently utilize clomiphene citrate and human menopausal gonadotrophins (hMG) to achieve multiple follicular development. In many patients premature luteinization or spontaneous onset of a luteinizing hormone (LH) surge lead to cancellation of planned oocyte recovery.

Continued administration of long-acting LH-releasing hormone agonists ($LHRH_A$) in women with regular menstrual cycles will induce hypogonadotrophic hypogonadism (Shaw *et al.* 1983; Lemay *et al.* 1984) and then it should be possible to control more precisely follicular growth under exogenous gonadotrophin stimulation. The aim of this study was to assess the benefits of such a treatment approach in an IVF programme, and also to assess the role of follicle stimulating hormone (FSH) and LH in follicular development by administering purified FSH (Metrodin, Serono, UK) alone to induce folliculogenesis.

Subjects and methods

The study included 13 women taking part in our IVF programme, they had regular ovulatory menstrual cycles between 26 and 31 days duration and bilateral tubal damage. Their ages ranged between 26 and 34 years (mean 31·4 years).

Treatment with the LHRH agonist D-Ser $(tBu)_6$-des-Gly-LHRH ethylamide (Buserelin, Hoechst) started on day 22 of the menstrual cycle; 100 μg was administered intranasally at 07.00, 11.00, 15.00, 19.00 and 23.00 hours and treatment was continued until the day of human chorionic gonadotrophin (hCG) administration. Fourteen days after the start of Buserelin

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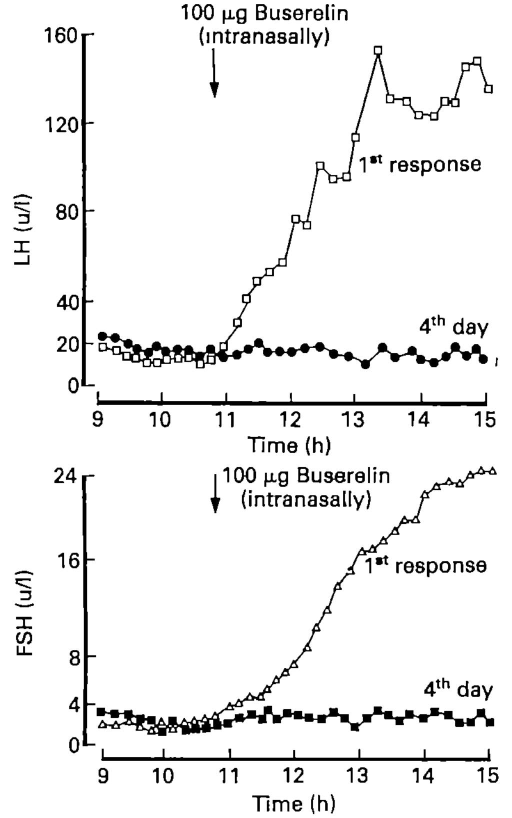

Fig. 1. Acute gonadotrophin release after first administration of 100 µg Buserelin intranasally on day 22 of cycle and response on fourth day of treatment at a dosage of 100 µg 4-hourly.

therapy (day 36 of cycle = day +1), two ampoules of purified FSH (Metrodin, each ampoule containing 75 i.u. FSH and 1 i.u. LH) were injected intramuscularly daily and this treatment was continued until the leading follicle(s) achieved a mean diameter of at least 15 mm as seen on ultrasound scan. No further FSH was then administered and 5000 units of hCG were given 1 or 2 days later, depending upon size and number of follicles, with laparoscopic oocyte collection performed 32–34 h after hCG administration. Venous blood samples (10 ml) were taken at 09.30 hours before drug administration on days 22, 23, 26, 29, 32, 35, +1, +3, +5, +7, +9 and alternate days until oocyte recovery. Serum was stored at −20°C and all samples for any individual patient were analysed in the same assay run for measurements of serum LH, FSH and oestradiol-17β (E_2). A sample for serum progesterone was taken 7 days after oocyte recovery.

In one patient the acute gonadotrophin release was assessed by taking venous blood samples (4 ml) every 10 min for 90 min before and 270 min after the administration of the first 100 µg intranasal dose of $LHRH_A$ and again on day 4 of administration (day 26 of cycle).

Pelvic ultrasound scans were performed on day 22, +1, +7, +9 and alternate days until oocyte recovery.

Assays

Oestradiol-17β was analysed using a non-extraction radioimmunoassay kit (Code ER-155, Steranti Research Ltd) with inter- and intra-assay coefficients of variation of 6·6% and 5·4%. Progesterone was measured in serum in our assay with interassay coefficients of variation of 9·5%.

Results

A marked LH and FSH response was observed following the administration of the first 100 µg of Buserelin intranasally. By 3 h, the LH rise appeared to have reached a plateau but the endogenous pulsatile release was still discernible. The FSH levels were still increasing at 4½ h when the acute study ended. Following this initial stimulated release there appeared to be a gradual reduction in circulating gonadotrophin levels. On day 4 of administration, a further study of acute response to $LHRH_A$ administration induced no significant rise in serum LH and no discernible increase in FSH although basal levels were still above baseline for LH (Fig. 1).

By day 29 (7th day of $LHRH_A$) mean serum LH and FSH were below pretreatment values for the group and remained so until FSH treatment was commenced. Serum E_2 values were suppressed to postmenopausal values (<100 pmol/l) in 10 of the 12 subjects by day 32 (10th day of treatment) and menstruation commenced between days 27 and 35.

Ultrasound scans showed that on day +1 (the beginning of Metrodin therapy) the ovaries were quiescent except in one patient in whom a cyst 5·2 cm diameter had been seen on day 22. This cyst increased in size on $LHRH_A$ therapy to 7·9 cm diameter on day 35. LHRH agonist treatment was discontinued and Metrodin was not given. Hormonal data from this patient were excluded from analyses and the cyst disappeared

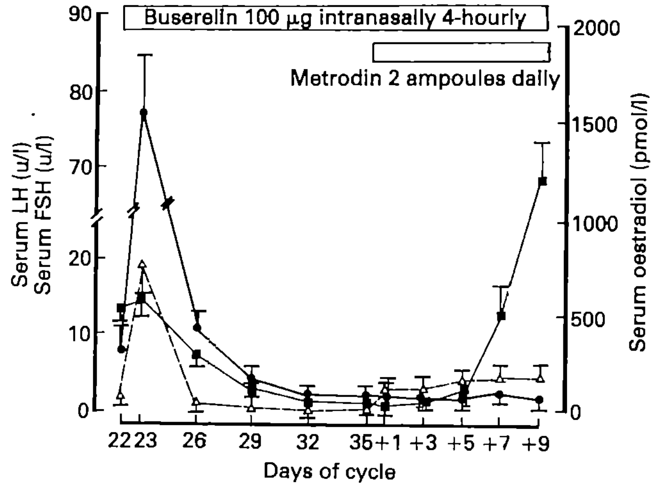

Fig. 2. Mean (+ SEM), serum LH (●), FSH (△) and oestradiol-17β (■) levels in 12 patients receiving Buserelin 100 µg intranasally 4-hourly, with commencement of 150 i.u FSH after pituitary desensitization to induce folliculogenesis.

spontaneously on day 45 when menses commenced.

Mean serum FSH values were more than double pretreatment levels after the start of purified FSH treatment ($P<0{\cdot}05$) whilst serum LH levels remained significantly reduced ($P<0{\cdot}05$) (Fig. 2).

The number of follicles stimulated and the duration of administration of FSH was extremely variable between individuals and this was reflected in the circulating E_2 values. The peak serum E_2, number of follicles (greater than 16 mm diameter), number of oocytes recovered and outcome of IVF are summarized in Table 1.

In 11 of the 12 patients mature pre-ovulatory oocytes were recovered. One patient failed to show any ovarian response after 14 days of stimulation and FSH treatment was discontinued. In eight patients a total of 24 embryos were transferred and four patients became pregnant, an indication of the viability of the embryos.

The mean serum progesterone level was 41·6 (SE 12·4) nmol/l 7 days after oocyte recovery. Surprisingly one of the patients who conceived with twins had a serum progesterone value of only 15 nmol/l 7 days after oocyte collection. Menstruation commenced between days +25 and +29 in the patients who did not become pregnant indicating a luteal phase of between 12 and 15 days with no additional hCG support being given. Since serial progesterone levels were not estimated we cannot comment on whether any luteal phases were inadequate.

Discussion

This study confirms that despite inducing pituitary desensitization by administration of a potent LHRH agonist, appropriate replacement with purified FSH alone can induce multifollicular development. The present study differs from that previously reported by Porter *et al.* (1984) in respect of the timing of the start of $LHRH_A$ treatment, by its mode of administration and the use of significantly less FSH to achieve mature pre-ovulatory follicles. However, their selection of patients for treatment was different—our patients were not chosen because of known previous poor responses to other treatment regimens and none of our patients had polycystic ovary syndrome.

At the beginning of $LHRH_A$ treatment, there is a phase of increased gonadotrophin secretion lasting some days, as previously reported in postmenopausal patients (Shaw *et al.* 1985) and in women with normal regular menstrual cycles (Meldrum *et al.* 1982; Lemay *et al.* 1984). However, fairly rapidly pituitary desensitization to the $LHRH_A$ was induced with levels of circulating gonadotrophins significantly lower than the mean for the early follicular phase and refractoriness to $LHRH_A$ administration was

Table 1. Number of days of FSH treatment, peak oestradiol, number of oocytes and outcome of embryo transfer

Patient no.	FSH treatment No. of days	 No. of ampoules	Peak oestradiol-17β (pmol/l)	No. of follicles ≥16 mm diameter	No. of oocytes recovered	No fertilized (No. transferred)	Outcome
1*	14	28	68	None	—	—	Menses, day +36
2	9	18	926	4	2	Nil (0)	Menses, day +26
3	9	18	1680	3	2	Nil (0)	Menses, day +29
4	10	20	2180	8	6	4 (3)	Menses, day +27
5	12	24	2378	9	6	4 (4)	Singleton birth, 34/40
6	15	30	2575	5	4	3 (3)	Twin birth 39/40
7	10	20	3010	5	3	1 (1)	Menses, day +25
8	12	24	3244	4	7	4 (4)	Menses, day +27
9	11	22	4128	9	2†	Nil (0)	Menses, day +28
10	10	20	4535	4	8	4 (4)	Twin birth, 34/40
11	8	16	4940	11	9	8 (4)	Spontaneous abortion, 8/40
12	10	20	4950	5‡	20	10 (4)	Menses, day +25

*Patient 1 failed to show ovarian response after 14 days and treatment was discontinued.

†Right ovary inaccessible, oocytes from left ovary only

‡Numerous others <15 mm. Patient readmitted with mild hyperstimulation 5 days post-oocyte recovery.

induced with serum oestradiol-17β levels suppressed to the postmenopausal range.

Administration of purified FSH (Metrodin) even on a relatively low dosage regimen induced multiple follicular growth patterns. However, in comparison to our other ovulation induction regimens (combining clomiphene citrate and hMG) significantly greater numbers of ampoules of FSH were required to reach mature follicular diameter, increasing overall costs of the treatment regimen.

LH levels were significantly lower than those seen in the normal follicular phase of the cycle after some 7 days of $LHRH_A$ therapy. Thus while we were unable to inhibit LH secretion completely, the study does question the need for any large quantities of LH in the process of folliculogenesis.

It is known that $LHRH_A$ administered in the luteal phase of the cycle can induce luteolysis (Sheehan *et al.* 1982). In addition binding of LHRH analogues to receptors have been reported in the human corpus luteum (Popkin *et al.* 1983). Theoretically then, luteal insufficiency could be induced by the use of $LHRH_A$. We are unable to comment on detailed luteal function in this study, but the serum progesterone level 7 days after oocyte collection was lower than that seen in other groups of patients undergoing IVF on our clomiphene and gonadotrophin regimen where the mean progesterone level 7 days after oocyte collection was 68·4 (SE 10·5) nmol/l ($n = 68$). Despite this possibility, pregnancies were established and the need to administer hCG for luteal phase support will need further assessment.

Further studies are required to assess the speed of pituitary desensitization, whether beginning $LHRH_A$ therapy at a different stage in the cycle or at different frequencies achieves this more rapidly or whether alternative dosage regimens and modes of administration may be more effective. These approaches, however, will allow new studies of folliculogenesis to be undertaken in an effort to determine the importance and amount of FSH and/or LH required. In addition the continued administration of hCG ensures that premature LH surges do not occur, and may significantly reduce the frequency of cancellation of oocyte recovery because of premature ovulation.

Acknowledgments

Our thanks to Dr P. Magill (Hoechst Pharmaceuticals UK) for supplying the Buserelin, and to Dr E. Snitcher (Serono UK) for providing the Metrodin and Profasi (hCG) for use in this study.

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Received 29 August 1986
Accepted 31 January 1987

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 687–691

An immunohistochemical study of steroid binding by endometrial glandular epithelial cells throughout the menstrual cycle

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Summary. An immunohistochemical technique was used to demonstrate oestrogen and progesterone binding by endometrial glandular epithelial cells at various stages of the menstrual cycle. A cross-section of steroid binding sites, including low affinity, concentration dependent Type II and III binding sites, were demonstrated but only in cells which contain the classical high affinity receptor. The technique demonstrated both free binding sites and receptor-hormone complexes within the cytoplasm but was poorly effective in demonstrating nuclear complexes. Oestrogen binding sites were shown to reach a peak during the late proliferative and early secretory phases of the cycle: oestrogen binding capacity remained high during the mid and late secretory phases. Progesterone binding capacity rose progressively throughout the proliferative and early secretory phase.

Cyclical variations in oestrogen and progesterone receptor concentrations in the normal human endometrium have been demonstrated by biochemical cytosol assays (Limpaphayom *et al.* 1971; Evans *et al.* 1974, Pollow *et al.* 1975; McLaughlin & Richardson 1976; Bayard *et al.* 1978; Sanborn *et al.* 1978; Spona *et al.* 1979; Rodriquez *et al.* 1979; Martin *et al.* 1979; Levy *et al.* 1980; Punnonen *et al.* 1984). Assays of this type do not, however, allow for cellular localization of the hormone receptors and do not distinguish between stromal and epithelial cell receptors. Further disadvantages of these assay systems include their cost, in terms of both equipment and time, and their requirement for fresh tissues.

The present study has aimed to overcome the inherent disadvantages of the biochemical assay systems by using an immunohistochemical technique to demonstrate oestrogen binding (EB) and progesterone binding (PB) sites in the normal cyclical endometrium, with particular reference to their concentrations in the functionally important component of this tissue, namely the endometrial glandular epithelium

Materials and methods

Material

Thirty-one histologically normal endometria were studied for the presence of EB sites and 34 for PB sites. These were obtained from premenopausal women (age range 30–48 years) who had undergone hysterectomy for non-endometrial disease, usually for uterine leiomyomata. All the tissues had been formalin fixed and the endometria had been 'dated' by

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using the histological criteria of Noyes *et al.* (1950).

Lung and lymph nodes, used for negative tissue controls, were obtained from autopsy material.

Reagents

Progesterone, oestradiol and rabbit anti-sera to oestradiol and progesterone were purchased from Calbiochem-Behring Corp.: tamoxifen, from Sigma Chemical Co. and diaminobenzidine tetrahydrochloride from Aldrich Chemical Co. The remaining immunological reagents were purchased from Dako Immunoglobulins Ltd.

Methods

Paraffin embedded sections, 5 µm thick, were assayed immunocytochemically for detection of hormone binding using the double PAP method described previously by Al-Timimi *et al* (1985). In brief, the sections were deparaffinized in xylene and rehydrated through graded alcohols. Endogenous peroxidase activity was blocked by immersing the sections in absolute methanol containing 0·5% hydrogen peroxide for 30 min. The sections were subsequently washed, first in running tap water and then in 0·05 M Tris-buffered saline (TBS) at pH 7·6. Non-specific background staining was reduced by covering the slides with a 1:10 dilution of normal swine serum (NSS) for 30 min. Excess of NSS was drained off and the sections then incubated with the appropriate hormone (oestrogen or progesterone) at concentrations 0·1 mg/ml to 0·01 mg/ml in TBS with (vol/vol) 1% ethanol overnight at 4°C in a moist chamber. After a very gentle rinse the hormones were stabilized at their binding sites with 1% paraformaldehyde for 5 min. After a wash in TBS the sections were incubated overnight at 4°C with the primary antiserum (rabbit anti-oestradiol at a dilution of 1:50 or rabbit anti-progesterone at a dilution of 1·25). After a thorough wash in TBS the sections were incubated sequentially with swine anti-rabbit immunoglobulin (SAR) diluted 1:25 for 30 min, horseradish peroxidase with rabbit anti-horseradish peroxidase (PAP) soluble complex 1:100 for 30 min, SAR 1.50 for 15 min and PAP 1:100 for 15 min. The sections were washed with TBS after each exposure to SAR or PAP. The bound hormones were demonstrated by incubating the slides for 5 min with a freshly prepared solution of 50 mg of diaminobenzidine (DAB) in 100 ml of TBS to which was added 0·02 ml of 30 vol hydrogen peroxide per 100 ml of substrate solution: the slides were then counterstained with haematoxylin, dehydrated and mounted.

Specificity controls

Tissue controls. Sections from normal lung and lymph nodes were used as negative tissue controls.

Method controls. In every staining run one component of the sequential staining reaction was omitted from at least one section, this usually being the omission of the specific rabbit antiserum and its replacement by normal rabbit serum.

Blocking controls. In each staining run for EB sites one section was pretreated with tamoxifen to block the EB sites.

Absorption controls. These were prepared by mixing a purified hormone preparation with the antiserum to this hormone for 24 h at 4°C before including the antiserum in the staining procedure.

Results

In all the endometria studied a considerable proportion of the epithelium showed binding sites for oestrogen and progesterone. All the control sections showed a complete absence of positive staining (Fig. 1). Pre-incubations of section with tamoxifen resulted in a marked decrease in staining for EB.

The staining of endometrial epithelial cells for EB and PB was characteristically diffuse and intracytoplasmic whilst only relatively rarely was núclear staining noted. Sub- or supranuclear vacuoles within the epithelial cells showed consistently negative staining reactions.

The percentage of EB-positive epithelial cells was low at the beginning of the cycle (lowest value 40%) but increased thereafter to reach a peak (virtually 100%) during the late proliferative and early secretory stages of the cycle (Fig 2). There was a slight fall in the percentage of EB-positive cells during the mid-secretory phase but the proportion of such cells rose again slightly during the late secretory phase.

The results obtained for PB-positive cells (Fig. 3) were rather more variable than were those obtained for EB-positive cells, but in

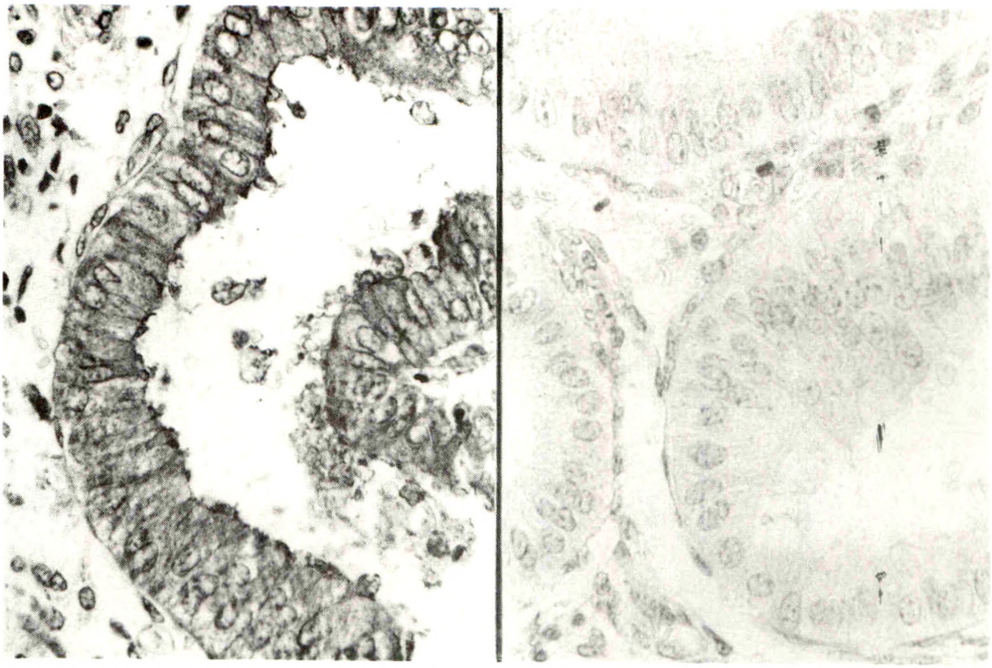

Fig. 1. On the left is endometrium stained for oestrogen-binding sites. On the right is a control section in the preparation of which the anti-oestrogen antibody had been absorbed by prior incubation with purified oestrogen × 440.

general, the percentage of positively staining epithelial cells tended to increase throughout the proliferative and early secretory phases of the cycle (from about 35 to 95%).

Discussion

Immunohistochemical techniques for demonstrating steroid hormone receptors have been criticised on the grounds that steroid hormones, when used in high concentration, attach to both specific receptors and to non-specific binding sites and that formalin fixation can lead to loss of steroid binding activity Chamness *et al.* 1980; Zehr *et al.* 1981; McCarty *et al.* 1981; Underwood 1983). It has been clearly shown that formalin fixation does not reduce steroid-binding capacity (Shimizu *et al.* 1983; Bennington 1983; Garancis *et al.* 1983; Al-Timimi *et al.* 1985) but it is readily admitted that immunohistochemical techniques almost certainly demonstrate not only Type I binding sites (the classical receptors measured in biochemical assays) but also Type II and III binding sites. These latter binding sites are not recognized in cytosol assays and are of a low affinity nature, their binding of hormone thus being concentration dependent. The physiological role of Type II and III binding sites is unknown but they are not present in non-target tissues and do appear to be specific recognition sites (Al-Timimi *et al.* 1985). Further, incubation of target tissues with increasing concentrations of a hormone fails, in immunohistochemical studies, to increase the proportion of cells showing a positive staining (Gunduz *et al.* 1983). Thus Type II and III binding at high ligand concentrations

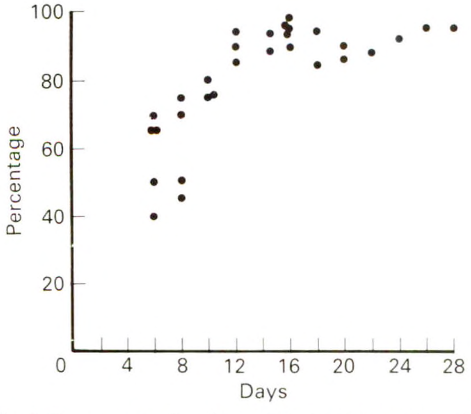

Fig. 2. Percentage of endometrial glandular cells staining postively for oestrogen-binding sites throughout the menstrual cycle.

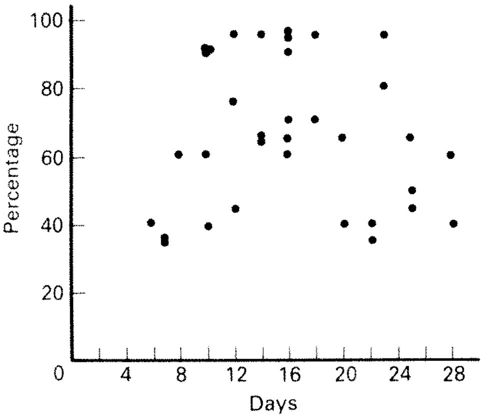

Fig. 3. Percentage of endometrial glandular cells staining positively for progesterone-binding sites throughout the menstrual cycle.

occurs only in cells that also contain Type I receptors. Immunohistochemical techniques recognize therefore, albeit indirectly, only those cells containing specific hormone receptors but possibly demonstrate a wider cross-section of binding sites than do cytosol assays.

Cytosol assay systems for hormone receptors do not usually recognize hormone-receptor complexes either within the cytosol or in the nucleus and hence show not what a hormone is doing but what it is not doing (Jansen & Shearman 1981). Current receptor theory suggests that anti-hormone antibodies cannot react with receptor-bound hormones, it being proposed that the hormone is enveloped in a hypothetical receptor cavity and bound at multiple sites, thus making the hormone unavailable to antibody (Underwood 1983). It is, however, possible, within the context of such a model, to postulate that binding proteins react with only a portion of the steroid molecule and in a previous study we have shown that the technique employed here does demonstrate endogenous bound hormone (Al-Timimi *et al.* 1985), thus giving a more complete picture of cell receptor status than do cytosol assays. It is admitted that the immunohistochemical technique does not appear to be very effective in demonstrating nuclear complexes but this is a fault that it shares with the biochemical assay system.

Our finding that peak levels of EB and PB within the endometrium occur during the late proliferative and early secretory phases of the menstrual cycle is in accord with most previously reported biochemical assay studies though the lack of a significant decline in EB levels during the mid and late secretory phases has been noted in only a few such reports (Pollow *et al.* 1975; Bayard *et al.* 1978; Punnonen *et al.* 1984). Comparison of our results with those obtained by assay techniques is, however, not strictly valid for we have documented only the binding status of epithelial cells whilst biochemical techniques also measure the receptor status of unknown proportions of stromal cells.

To the best of our knowledge there have been only two previously reported histologically-based studies of variations in hormone-binding capacity of the endometrium throughout the menstrual cycle and, because of methodological differences, it is also difficult to compare their results with those obtained in this investigation. Press *et al.* (1984) employed a monoclonal antibody to oestrogen receptor but were able to demonstrate only intranuclear staining whilst Bergqvist *et al.* (1985), using a cytochemical technique and employing fluorochrome-labelled steroids, did note that glandular epithelial fluorescence tended to be less intense during the later stages of the cycle.

The endocrinological basis for variations in endometrial steroid receptor levels during the menstrual cycle appears to be well defined and results from an interplay between the capacity of oestrogens to induce both oestrogen and progesterone binding sites, the anti-oestrogenic effects of progesterone and the translocation of receptor-hormone complexes to the nucleus (Jansen & Shearman 1981), but other factors are almost certainly involved. Thus Punnonen *et al.* (1984) noted that endometrial oestrogen receptor levels were much higher in Finnish than in Japanese women and that a significant difference in receptor levels between the proliferative and secretory phases of the menstrual cycle was apparent only in the Finnish women. Wagner & Jungblut (1980) showed that in rats deprived of endogenous hormones by oophorectomy and hypophysectomy, endometrial oestrogen receptors were still synthesized, their levels showing irregular fluctuations with a periodicity of 6–9 days. Clearly, therefore modulation of endometrial steroid binding capacity is influenced by, as yet unidentified, non-hormonal influences.

We conclude that further study of variations in endometrial steroid binding capacity can be undertaken using an immunohistochemical technique, a valid method which has many advantages over biochemical cytosol assays.

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Received 7 July 1986
Accepted 16 September 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 692–695

The clinical significance of pre-operative serum CA 125 in ovarian cancer

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Summary. In a prospective study of 52 patients with ovarian malignancy followed up for 3–18 months the clinical significance of pre-operative serum CA 125 as a tumour marker was assessed. In 41 patients with epithelial ovarian cancer, the level of CA 125 correlated well with tumour load as indicated by FIGO stage. All epithelial histological types, including mucinous, released CA 125 although serous and undifferentiated tumours produced quantitatively more antigen. There was, however, no correlation between CA 125 concentration and histopathological grade, nor did CA 125 level appear to be of any prognostic value in epithelial ovarian cancer. Elevated CA 125 levels were also found in patients with sex cord/stromal tumours, Krukenberg tumours, an ovarian sarcoma and a serous carcinoma of low malignant potential.

Ovarian cancer accounts for more deaths annually than cancer of the uterine cervix and corpus together (Hudson 1985). In the early stages, it is asymptomatic and undetectable Indeed, 70% of patients have metastases beyond the pelvis at diagnosis (Piver 1983). The natural history also precludes accurate monitoring of disease status; consequently, second-look laparotomy is advocated (Cohen *et al.* 1983), although this is an invasive procedure with an inherent morbidity. It is not associated with any survival advantage and the inability to exclude residual or distant micrometastases is illustrated by the relapse rate among patients with complete surgical response.

The existence of effective therapy accentuates the need for a sensitive tumour marker in this concealed disease. The value of tumour markers has already been established in gynaecological oncology. In ovarian germ cell tumours and gestational choriocarcinoma, estimation of α-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and Schwangerschafts-protein 1 (SP_1) provide a quantitative assessment of viable tumour load (Bagshawe 1976; Talerman *et al.* 1978). In the context of epithelial ovarian cancer, several potential markers have been investigated (Khoo & MacKay 1973; Seppala *et al.* 1975; Knauf & Urbach 1978) Of these, the antigenic determinant, CA 125, appears to be the most useful clinically with a reported sensitivity of 82% and a concordance with disease status of 93% (Bast *et al.* 1983; Canney *et al.* 1984; Dodd *et al.* 1985). These studies, however, dealt largely with post-operative sera from patients with poorly quantified persistent or recurrent disease The aim of this study was to investigate the clinical significance of pre-operative CA 125, for which published data are lacking particularly with regard to early stage disease (Canney *et al.* 1984)

CA 125 is defined by a murine IgGl monoclonal antibody raised against the serous ovarian carcinoma cell line OVCA 433 (Bast *et al* 1981). An immunoradiometric assay has been developed to detect CA 125 in serum (Klug *et al.* 1984).

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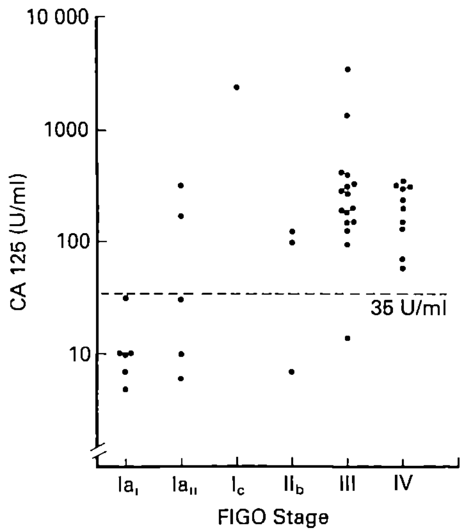

Fig. 1. Pre-operative serum CA 125 in 41 patients with epithelial ovarian carcinoma related to FIGO stage Stages I + II vs III + IV: $P<0{\cdot}0001$, ($t = 4\ 45$; d.f $= 39{\cdot}0$) Note log scale of y axis

Subjects and methods

Pre-operative sera were collected prospectively between 1 and 7 days before surgery from 52 patients who had ovarian cancer subsequently confirmed histologically after primary cytoreductive surgery. Intra-operative staging was according to the FIGO classification while histopathological classification and grading of tumours was according to World Health Organization (WHO) criteria. Those patients with FIGO Stage Ia(ii) disease or more received chemotherapy according to the protocol of a randomized multicentre trial. Assessment of tumour response was according to the WHO (1979) criteria. Those who demonstrated a complete or partial response were designated as responders and those with stable disease, progressive disease or who died of disease were classified as non-responders. Follow-up was from 3 to 18 months.

Assay

Serum samples were separated into aliquots and stored at −40°C. They were assayed blind by D.C and had not been previously thawed. The commercially available kit (CIS UK Ltd, London) used to measure serum CA 125 is a simultaneous sandwich solid-phase immunoradiometric assay. The inter- and intra-assay coefficient of variation were 11·2% and 7·5%, respectively (Klug *et al.* 1984). A level of ≥35 U/ml was taken to represent a positive result (Bast *et al.* 1983).

Student's t-test with logarithmic transformation was used to determine statistical significance.

Results

Of the 52 patients, 41 had epithelial ovarian carcinomas. Positive results were more frequent in the patients with advanced disease and there was a correlation between the absolute CA 125 level and viable tumour load (FIGO stage) (Fig. 1). None of the patients with Stage Iai disease shed the antigen in significant amounts pre-operatively. The patient with a Stage III tumour who did not have an elevated CA 125 pre-operatively had a mucinous carcinoma, and CA 125 rose to 74 U/ml on the third postoperative day. Of the 10 patients with Stage I and II disease and CA 125 <35 U/ml before surgery, four with non-mucinous tumours had a transient acute elevation of CA 125 in the postoperative period (range 83–103 U/ml) between days 6 and 16. The overall sensitivity of pre-operative serum CA 125 in this series was 73% (peri-operative sensitivity of 85%) with a sensitivity in Stage III and IV disease of 96% (peri-operative sensitivity of 100%).

With regard to histopathology (Table 1) the four patients with serous adenocarcinomas and negative sera had Stage Iai disease Although there was no significant difference between the histological types in terms of CA 125 expression, the serous and undifferentiated tumours

Table 1. Histopathology and pre-operative serum CA 125 in 41 patients with epithelial ovarian carcinoma

		Patients with positive CA 125 levels (> 35 U/ml)	
Histology	No of patients	n (%)	CA 125 (U/ml) Mean (SD)
Serous	13	9 (69)	616 (809)
Mucinous	9	5 (56)	211 (129)
Endometrioid	2	2 (100)	243 (123)
Clear cell	4	2 (50)	116 (21)
Undifferentiated	13	12 (92)	530 (978)
Total	41	30 (73)	

Table 2. Pre-operative serum CA 125 in 11 patients with non-epithelial primary ovarian malignancies and tumours of low malignant potential

Histology	*n*	FIGO stage	CA 125 (U/ml)
Sex cord stromal tumour	3	Iai	16
		Iaii	86
		Iaii	304
Immature teratoma	1	Iai	31
Sarcoma	1	III	122
Krukenberg tumour	2	—	90
		—	113
Carcinoma of low malignant potential			
Serous	2	Iai	30
		Ic	327
Mucinous	2	Iai	12
		Iai	14

appeared to release more antigen. There was no correlation between CA 125 and histopathological grade.

The pre-operative CA 125 level did not predict disease outcome in epithelial ovarian cancer. There was no significant difference in the pre-operative CA 125 levels between responders and non-responders as defined by clinical status at last presentation

The remaining 11 patients in this group had non-epithelial ovarian primaries or tumours of low malignant potential (Table 2).

Discussion

In this study the earliest stage of disease which released significant amounts of CA 125 pre-operatively was FIGO Iaii (two of five patients). None of the six patients with Iai disease had elevated serum CA 125 values pre-operatively. This may be because the malignant epithelium expressing CA 125 in Iai disease is confined within a fibrous capsule barrier and only when it is breached (Iaii) is antigen free to enter the vascular space. Alternatively, the threshold of tumour volume detection with CA 125 may be associated with a tumour volume greater than that found in Iai disease. This would be in keeping with the findings of Niloff *et al.* (1985) that 22 of 36 patients with CA 125 <35 U/ml had residual tumour <1 cm at second-look procedure. A significant correlation with stage at presentation suggests that the CA 125 level reflects tumour volume.

The sensitivity of pre-operative CA 125 in epithelial ovarian cancer was 73% in this series, although from peri-operative data at least 85% of the tumours expressed CA 125 This provides a more accurate reflection of the natural expression of CA 125 in patients with ovarian cancer compared with previous studies which included only or mainly patients with persistent or recurrent disease Our study was based on an unselected population and Stages I and II were well represented. Ricolleau *et al.* (1984) confined their study to postoperative patients with Stage III and IV disease and reported a sensitivity of 92% compared with 100% in a comparable group in the present series. In agreement with Canney *et al.* (1984) CA 125 was elevated in all histological types, including mucinous tumours which were originally reported as negative, both immunohistologically (Kabawat *et al.* 1983) and serologically (Bast *et al.* 1983). The lack of correlation between CA 125 and histopathological grade agrees with the immunohistopathology findings of Kabawat *et al.* (1983) and suggests that CA 125 is not a tumour differentiation antigen. Although pre-operative CA 125 does not appear to predict disease outcome as defined by response, long-term follow-up will be necessary to see if there is a difference in terms of survival.

The value of CA 125 in non-epithelial ovarian malignancy warrants further examination as values >35 U/ml were found in two sex cord/stromal tumours (in contrast to the findings of Kabawat *et al.* (1983)) and a sarcoma pre-operatively

In conclusion, the tumour marker CA 125 has the potential to influence the management of ovarian cancer. Further investigation, however, is warranted particularly in relation to the limit of tumour volume detection in individual patients. This has implications for the possible use of CA 125 as a screening test.

Acknowledgments

This study was supported by the E. J. Smith Executory, Grampian Health Board. CA 125 kits were donated by CIS UK Ltd. We are grateful to Professor A. A. Templeton and Dr P. B. Terry for their support and advice during the study and in the preparation of this paper. We would also like to acknowledge the help of the gynaecological residents, the nurses at the com-

bined clinic and the staff at the blood transfusion service.

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Received 12 September 1986
Accepted 18 November 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol 94, pp. 696–698

Independent expression in serum of three tumour-associated antigens: CA 125, placental alkaline phosphatase and HMFG2 in ovarian carcinoma

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Summary. Circulating levels of CA 125, the HMFG2 antigen and placental alkaline phosphatase were measured in patients with epithelial ovarian cancer. In 37 patients the antigens were assayed before operation and 161 follow-up samples from 41 patients were assayed at different times during treatment. These three human tumour-associated antigens were expressed independently of each other. Measurement of all three antigens, compared with measurement of CA 125 alone, resulted in a statistically significant improvement in the detection rate of patients with localized disease from 18% to 69%.

In the past 5 years, monoclonal antibodies to many ovarian cancer-associated antigens have been described and are being assessed clinically for use as agents in immunocytochemistry, immunohistology, radioimmunolocalization and antibody targetted tumour therapy. Several have been used to detect levels of circulating antigen in patients with this disease in an attempt to discover a clinically useful serum marker. The yardstick to which such markers can be compared is CA 125, a high molecular weight glycoprotein present in the serum of approximately 80% of patients with active ovarian cancer compared within only 1–5% of normal controls (Bast *et al* 1983; Canney *et al.* 1984; Crombach *et al.* 1985). However, in patients in apparent complete clinical remission, normal levels of CA 125 are not predictive of the absence of microscopic disease (Atack *et al.* 1986). No data have been published on the levels of CA 125 in early (stage 1) disease, so the value of the test for screening is unknown.

The monoclonal antibody HMFG2 defines an antigen also present on a tumour-associated high molecular weight glycoprotein. Immunohistological studies have shown the antigen to be present in 94% of ovarian carcinomas of all histological subtypes (B. G. Ward *et al.* unpublished observations). The antigen has also been shown to be detectable in the serum of 62% of patients with all stages of ovarian cancer (Burchell *et al.* 1984; Ward & Cruickshank 1987). Placental alkaline phosphatase (PLAP) is a tumour-associated enzyme present on the tumour cells of between 30 and 100% of patients with ovarian carcinoma and in the serum of between 30 and 60% of patients with active disease (McDicken *et al* 1985; Davies *et al.* 1985*a*; Nouwen *et al.* 1985).

Recently, the similarity of expression of PLAP and CA 125 in normal malignant tissues has been noted (Davies *et al.* 1985*b*). There are, however, sufficient dissimilarities of expression in these tissues to suggest the antigens detected

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are not the same (Niloff *et al.* 1985). The aims of this study were to determine the relation between the expression of these three antigens in individual patients and to assess a combination of antibodies for use as a potential serum screen for ovarian cancer.

Subjects and methods

Serum samples

Serum samples were collected prospectively from patients attending the Gynaecology Department, Royal Infirmary, Aberdeen. Pretreatment samples from 37 patients with ovarian carcinoma, as well as 161 follow-up samples from 41 patients, were collected. Clinical data including histopathological confirmation of diagnosis and stage at presentation and disease status at time of collection of follow-up samples were available. Serum samples were stored frozen and thawed once only for assays.

Assays for antigen expression

Samples were assayed for the HMFG2 antigen by a radioimmunometric assay as described previously (Ward & Cruickshank 1987). Using this assay a normal range (<1500 U) has been defined which includes 92% of a control population (Ward & Cruickshank 1987). Aliquots of the same samples were simultaneously assayed for PLAP and PLAP-like activity by colorimetric assays using the antibodies H317 and H17E2 as described by McLaughlin *et al.* (1983) and Tucker *et al.* (1985), respectively. These antibodies recognize PLAP phenotypes, both are tumour associated, however, PLAP-like activity (recognized by H17E2) is also elevated in the serum of smokers. In a normal non-smoking control population there is no circulating PLAP activity. CA 125 levels were estimated using a commercially available radioimmunometric kit assay (CIS, UK). Using this kit, a normal range (<35 U/ml) has been defined which excludes approximately 1% of a normal control population (Bast & Knapp 1985).

Table 1. Correlation coefficients between CA 125, HMFG2 antigen and placental alkaline phosphatase expression in the serum of patients with ovarian carcinoma (n = 198)

	HMFG2	H17E2	H317
CA 125	0·016	0·045	0·091
HMFG2	—	0·150	0·111
H17E2	—	—	0·732

Results

Pretreatment samples

Stages I and II. Pretreatment serum samples were available from 11 patients with localized disease. Using the CA 125 assay, two patients (18%) had elevated values; adding the HMFG2 and PLAP assays detected a further five patients (each assay identified three patients). Thus serial serum assays of the three antigens detected 7 of the 11 patients (64%) with localized ovarian cancer. This improvement was statistically significant (using McNemar's test with continuity correction gives a χ^2 value of P = 0·07). Only one patient had elevated values of more than one antigen.

Stages III and IV. Of the 26 patients with advanced disease 25 (96%) had elevated CA 125 levels. The patient with the normal CA 125 level also had normal levels of HMFG2 antigen but markedly elevated PLAP levels. Thus all patients with advanced disease had elevated levels of at least one of these markers preoperatively.

Relation between serum levels of CA 125, HMFG2 antigen and PLAP

The individual values of the total of 198 pretreatment and follow-up samples were plotted for each assay against each other assay and the correlation between individual values determined by Pearson's correlation coefficient. This method determined not only whether there was a relation between the expression or non-expression of the antigens but also whether there was a relation between the amount of expression of the other three. Table 1 shows that no relation was demonstrated between the expression of CA 125, the HMFG2 antigen and PLAP. The only significant correlation (0·732; P<0·001) was seen between the isotypes of PLAP defined by the monoclonal antibodies H317 and H17E2.

This analysis was also performed on single, randomly chosen samples for each patient with closely similar results demonstrating the same relations.

Discussion

Our data suggest that the expression of CA 125, the HMFG2 antigen and PLAP are independent of one another. In fact in 11 patients with localized ovarian cancer, only one patient had elevated serum levels of more than one of these tumour-associated antigens. This observation is particularly important in developing a screening test for this disease. Our use of serial assays for the three antigens improved the detection rate for localized disease before operation from 18% (using the CA 125 assay alone) to 64%. Of the other 26 patients with advanced disease, 96% had elevated CA 125 levels, the one patient who had a normal CA 125 level expressed PLAP.

Recent reports from Knauf *et al.* (1985) and Sekine *et al.* (1985) suggest that the tumour-associated antigens NB/70K and DF3 are also expressed independently of CA 125. Measurement of serum levels of these two antigens in addition to CA 125, HMFG2 antigen and PLAP may further improve the potential for detection of localized disease.

As yet data on the rate of false positive detection in a screening population are incomplete. For the purpose of screening, the false positive rate for all these antigens will need to be of the order of 0·1% in order that the predictive value of a positive test be at least 50%. At present the false positive rate of a single screen is 1% for CA125 (Bast & Knapp 1985), 8% for HMFG2 antigen (Ward & Cruickshank 1987), and for PLAP it is not yet known. Efforts are being made to decrease the false positive rate of HMFG2 antigen assay, and determine the rate for the PLAP assay. A prospective study in a general population can then be undertaken.

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Received 29 July 1986
Accepted 10 December 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol 94, pp 699–703

A retrospective review of adenocarcinoma-in-situ and glandular atypia of the uterine cervix

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Summary. Between 1978 and 1985, 19 cases of adenocarcinoma-in-situ and 12 cases of glandular atypia have been identified at the Birmingham and Midland Hospital for Women. In 19 cases an associated dysplastic squamous element was identified, 20 of 28 pre-diagnosis smears correctly predicted a glandular lesion, 5 of 17 colposcopically directed biopsies predicted the findings in a larger biopsy (cone biopsy or hysterectomy). Colposcopy provided no additional information with regard to diagnosis. Twelve of 13 patients managed by cone biopsy and 16 of 17 by abdominal hysterectomy have been treated successfully as defined by subsequent normal cytology.

Adenocarcinoma of the cervix is less common than its squamous counterpart, occurring with a frequency ranging from 5·5% (Abell & Gosling 1962) to 34% (Davis & Moon 1975). The incidence has also been observed to increase (Gallup & Abell 1977; Shingleton *et al.* 1981).

It has been postulated that, like squamous cell carcinoma, adenocarcinoma also has a pre-invasive or in-situ stage (Boon *et al.* 1981; Christopherson *et al.* 1979; Burghardt 1973). The diagnosis and management of glandular intraepithelial lesions is, however, much more problematic than for squamous lesions. The difficulties are explained in part by the rarity of the condition which has precluded an accumulated clinical experience, but also by the nature of the disease. It has been postulated that the whole endocervical canal may be a site for malignant transformation, the abnormality not being confined to a circumscribed transformation zone (Nguyen & Jeannot 1984). The standard diagnostic and therapeutic techniques employed in cervical intraepithelial neoplasia (CIN) might be considered inappropriate in this situation.

These problems have prompted an assessment of the cytological, colposcopic and histological diagnosis of all glandular dysplasias seen in our institution. Treatment outcome has also been assessed with a view to rationalizing future management protocols

Patients and methods

The case records of all patients found to have adenocarcinoma-in-situ or glandular atypia in any cervical biopsy taken between January 1978 and December 1985 were reviewed (these cases are collectively classified as glandular dysplasia). Cases where an associated invasive element was indentified were excluded. Cytology reports before and after diagnosis, details of colposcopic examination before and after diagnosis, and

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comparisons between histology reports, when more than one was available, were recorded, age, parity, recent obstetric history and contraceptive usage were also noted.

Two types of glandular abnormality were recognized; adenocarcinoma-in-situ (AIS) with or without coexistent squamous dysplasia, and glandular atypia (where epithelial changes were present but considered less than those seen in AIS), again with or without squamous dysplasia. These criteria identified 31 patients, 19 had AIS and 12 had glandular atypia. Diagnosis in all instances was by wedge, cone, or hysterectomy specimen.

Results

Clinical features

The median age, parity, recent obstetric history and contraceptive use in the two identified histological groups are shown in Table 1. Significantly fewer patients in the glandular atypia group used oral contraception ($0{\cdot}05>P>0{\cdot}02$, χ^2).

Biopsy types

The minimum biopsy on which diagnosis was based in this series was a wedge biopsy (one patient), the others had had either a cone biopsy or a hysterectomy. In 17 patients a colposcopically directed punch biopsy had been obtained before a larger biopsy and in five of them the punch biopsy diagnosis accurately reflected that seen in the larger biopsy. In the 12 false negative (for glandular dysplasia) punch biopsies, CIN was diagnosed on five occasions, early squamous invasion was suspected in two and no lesion was identified in the remainder.

Associated squamous lesions

Of the 31 patients, 18 (58%) had an associated dysplastic squamous element, either intermixed with or separate from the glandular lesions. Of the 19 patients with AIS, 11 had an associated squamous lesion and 7 of the 12 with glandular atypias had an associated squamous lesion The squamous lesions were all CIN (CIN III, 12; CIN II, 4; CIN I, 2) after large biopsies, although the directed punch biopsy had shown suspicion of invasion on two occasions.

Colposcopy

Of the 31 patients with glandular dysplasia, 27 had a colposcopic assessment before diagnosis. In four no abnormality was seen, in 16 squamous intraepithelial neoplasia was suspected, in five an invasive lesion was suspected, and in two glandular intraepithelial neoplasia was suspected (although in both, pre-existing cytology reports had suggested a glandular lesion). The colposcopist suspected CIN in 10 of 17 mixed glandular and squamous lesions and in 6 of 10 pure glandular lesions. The whole transformation zone was visible in 16 of 27 instances

Cytology

Of the patients with glandular dysplasia, 28 had at least one smear in the 12 months preceding diagnosis. Details of cytology are given in Table 2. Twenty cases had a smear suggestive of a glandular lesion (using cytologic criteria reported by Bousfield *et al.* (1980) and Boon *et al.* (1981)) giving an overall sensitivity of 71%. The sensitivity was noticably less for mixed lesions (58%) than for pure glandular lesions (91%).

Cytological sensitivity was not influenced by the severity of the glandular lesion, 14 of 19 adenocarcinomata-in-situ being correctly predicted and 6 of 9 glandular atypias being correctly predicted.

Management

Thirteen patients were managed by cone biopsy alone (6 AIS; 7 atypias); 17 were managed by

Table 1. Clinical features

Histology group	*n*	Age (years) Median (range)	No. of nulliparas	No. pregnant within 3 years	Oral contraceptive users
Adenocarcinoma-in-situ	19	35 (22–63)	2	7	12
Glandular atypia	12	36 (31–60)	2	2	2

Table 2. Cytology diagnosis based on any smear in preceding 12 months

	Suggestive of glandular abnormality	No suggestion of glandular abnormality
Pure glandular lesion	10	1
Mixed glandular and squamous	10	7

total abdominal hysterectomy (5 atypias, 12 AIS) and one patient with AIS had a wedge biopsy followed by radical diathermy (Table 3).

The median follow-up period in the 19 patients with AIS is now 36 months (range 4–84 months). Six were managed by cone biopsy (median follow-up 36 months), 12 by total abdominal hysterectomy (median follow-up 48 months) and one by radical diathermy after wedge biopsy. Two patients have developed evidence of residual glandular dysplasia during follow-up. Abnormal glandular cytology was noted in one patient 13 months after cone biopsy (12 mm long); AIS was confirmed at subsequent hysterectomy. In a second patient, abnormal glandular cytology was noted 12 months after hysterectomy, performed for AIS, and subsequent excisional vault biopsy has confirmed residual AIS. Seven patients with glandular atypia were managed by cone biopsy (median follow-up 24 months), five by hysterectomy (median follow-up 13 months). All patients remain cytologically free of disease.

Hysterectomy after cone biopsy

In 10 patients managed by hysterectomy a prior cone biopsy had been taken. Cone excision had been considered complete in two but residual AIS was seen in one of these hysterectomy specimens Incomplete excision had been noted in eight patients and the subsequent hysterectomy revealed residual disease in four of these. Six of the preceding cone biopsies had been considered therapeutic (>25 mm long) and two of the subsequent hysterectomies were positive for residual glandular disease. Four cone biopsies were considered diagnostic (<25 mm long) and three were positive for disease on subsequent hysterectomy

Discussion

Glandular dysplasia, although apparently less common than squamous dysplasia, is almost certainly an underdiagnosed lesion. We, along with others (Boon *et al* 1981; Qizilbash 1975; Christopherson *et al.* 1979; Ostor *et al* 1984), have noted the disparity in ratios between pre-invasive and invasive lesions with almost 25% of our surgically-managed cervical cancers having a glandular component, yet less than 1% of our pre-invasive lesions demonstrated malignant glandular elements.

Diagnosis of glandular dysplasia depends on cytological recognition or on a chance finding in a serially sectioned cone biopsy performed because of a suspected squamous lesion. Combined squamous and glandular lesions are not uncommonly seen (Christopherson *et al.* 1979; Brown & Wells 1986). In 71% of our cases at least one smear in the preceding 12 months had been suggestive of a glandular lesion, this sensitivity being similar to that reported by Nguyen & Jeannot (65%) (1984) and Ostor *et al.* (70%) (1984), although these authors included micro-invasive carcinomas in their series. It was also of interest to note the somewhat poorer sensitivity of cytology in the presence of an associated squamous lesion. This might be explained by the observation reported by Christopherson *et al.* (1979) of the squamous lesion predominating and being undifferentiated, both of which may cause a glandular component to be overlooked.

Our data confirm previously documented doubt concerning the reliability of directed punch biopsy in this condition (Christopherson *et al.* 1979; Oster *et al.* 1984) The poor perform-

Table 3. Clinical management and length of follow-up in 31 patients

Management	Number	Follow-up (months) Median (range)
Hysterectomy		
Adenocarcinoma-in-situ	12	48 (4–84)
Atypia	5	13 (4–60)
Cone biopsy/wedge and radical diathermy		
Adenocarcinoma-in-situ	7*	36 (12–71)
Atypia	7	24 (4–48)

* One patient had radical diathermy.

ance of directed punch is attributable to lack of criteria for colposcopic recognition and to the finding that lesions may be small and confined to a small area of the cervix (Weisbrot *et al.* 1972) sometimes high in the endocervical canal beyond the upper limit of the transformation zone (Nguyen & Jeannot 1984) These authors documented two out of nine instances of this phenomenon. It should also be stressed that it may be impossible to exclude invasive adenocarcinoma on a punch biopsy specimen. Colposcopy and directed biopsy have evolved toward the diagnosis and management of squamous dysplasia, and they have a limited role in glandular dysplasia.

The inclusion of glandular atypia in our series deserves some explanation. Glandular dysplasia of lesser degree than AIS is not universally accepted as pre-neoplastic but might be considered as such by morphometric criteria presented by Brown & Wells (1986) and Betsill & Clark (1986). Bousfield *et al.* (1980) also justified the inclusion of these lesions, termed endocervical dysplasia, by analogy with preneoplastic lesions identified in rectal glandular epithelium. In the absence of evidence to the contrary, all such atypical glandular lesions must be regarded with some degree of suspicion.

In considering management, it is important to realize that the condition is almost certainly frequently overlooked. Therefore one must accept that such techniques as cone biopsy and local destruction commonly employed to manage squamous lesions have also been inadvertently applied to undiagnosed glandular lesions. There are no reports to suggest a disproportionate number of glandular carcinomas after cone biopsy and one might suggest that such 'inadvertent' treatment has been successful. The arguments against cone biopsy being appropriate management are largely theoretical in that the presence of 'skip' lesions high in the endocervical canal have been recorded, albeit infrequently. Ostor *et al.* (1984) recorded such multifocal lesions in only 3 of 20 instances. In addition, high residual disease rates in hysterectomy specimens taken after cone have been reported (Christopherson *et al.* 1979; Weisbrot *et al.* 1972). In neither series were cone biopsy dimensions mentioned, nor were cone biopsy/hysterectomy intervals. Based on excision criteria, conization has been found to be effective in removing disease, Qizilbash (1975) reporting one patient case, Gloor & Ruzicka (1982) four, Betsill & Clark (1986) nine and Oster *et al.* (1984) another four patients.

Our own data, based on cytology follow-up criteria, suggest that cone biopsy (>25 mm long) may be appropriate management, although we would recognize that the residual disease found in our hysterectomy specimens provides cause for concern in that it cannot be accurately predicted by cone excision status or by cone biopsy length. Oster *et al.* (1984) recommended hysterectomy if the cone excision margins are seen to be involved with malignant glandular epithelium, 4 of 6 such cases having residual AIS in the hysterectomy specimen. Careful and close cytology follow-up is clearly indicated in patients managed by cone biopsy.

In conclusion, two points deserve emphasis. Efforts must aim to improve cytological recognition of this disorder since the postulated increase in frequency of the disease bears some relation to increased cytological awareness. Secondly, positive efforts to rationalize management are essential. The choice of treatment should be based upon data generated by objective assessment preferably within the context of controlled clinical trials.

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Received 22 July 1986
Accepted 25 November 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol 94, pp. 704–708

Pregnancy and delivery by caesarean section in a patient with transposition of the great arteries and single ventricle. Case report

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Case report

The patient was born at home in 1959, and at the age of 8 days, she developed feeding difficulties. Cardiac catheterization performed at the age of 6 months led to the diagnosis of a corrected transposition of the great arteries (TGA) with ventricular septal defect (VSD), mitral stenosis and pulmonary hypertension. In her early childhood, growth and development were normal and the patient was only slightly hindered in physical activities. A second cardiac catheterization at the age of 17 years confirmed a systemic-to-pulmonary shunt of 75%, a pulmonary-to-systemic shunt of 5% and normal pulmonary vascular resistance. Heart surgery was rejected on the grounds of the risks being too high. In later years she suffered from palpitations, dizziness and exertional dyspnoea, and in 1984 dyspnoea at rest also developed Dye dilution curve manifested an escalation of the pulmonary-to-systemic shunt to 24%. An echocardiographic study in 1984 led to a new diagnosis of the defect as: genuine transposition of the great arteries and (considering the size of the VSD) a single ventricle (Figs 1 and 2). The cardiologists raised no objections to a pregnancy in the presence of this congenital heart defect class II-III New York Heart Association (NYHA).

The slightly cyanotic woman (weight 52 kg, height 167 cm) was first seen at our polyclinic at 15 weeks gestational age. The haemoglobin was 15·6 g/dl, and the haemotocrit 44%. The patient took digoxin (Digoxin) 0·25 mg and isosorbide dinitrate (Sorbidilat) 80 mg daily. Except for a poor weight gain of 4·5 kg, pregnancy up to the 36th week was uncomplicated. Serial ultrasound measurements showed normal intrauterine growth. Oestriol and human placental lactogen (hPL) were within the normal range. At 36 weeks gestation the patient was admitted to the hospital because of increasing dyspnoea and central cyanosis.

At 38 weeks, labour was induced by prostaglandin E_2 because of intrauterine growth retardation. Because of persistent late decelerations the patient was delivered by caesarean section under epidural anaesthesia. Pre-operatively, arterial blood gas analysis showed a pH of 7·41, a $P\text{O}_2$ of 6·76 kPa, and an oxygen saturation of 86%. The operation progressed without complication, blood pressure remained within the normal range and blood loss was 400 ml. A male child weighing 2240 g was born, measuring 44 cm in length with a head circumference of 32 cm The infant was small-for-gestational age (SGA), all measurements were below the 10th centile. The Apgar scores were 8, 9 and 9 at 1, 5 and 10 min, respectively. Umbilical cord artery pH was 7·20, and the cord vein pH 7·30. The child showed no malformations. The placenta weighed 350 g and no infarctions were seen.

The postoperative course was uncomplicated. From the time of admission to hospital, the patient daily received 10 000 units heparin subcutaneously for prophylaxis against thrombosis; 72 h after the operation, thrombosis prophylaxis was switched to coumarin (Marcoumar) and continued for another 6 weeks. Amoxicillin (Ampicillin) and tobramycin (Obracin) were administered pre-operatively and continued for another 5 days. On the 18th day the patient was

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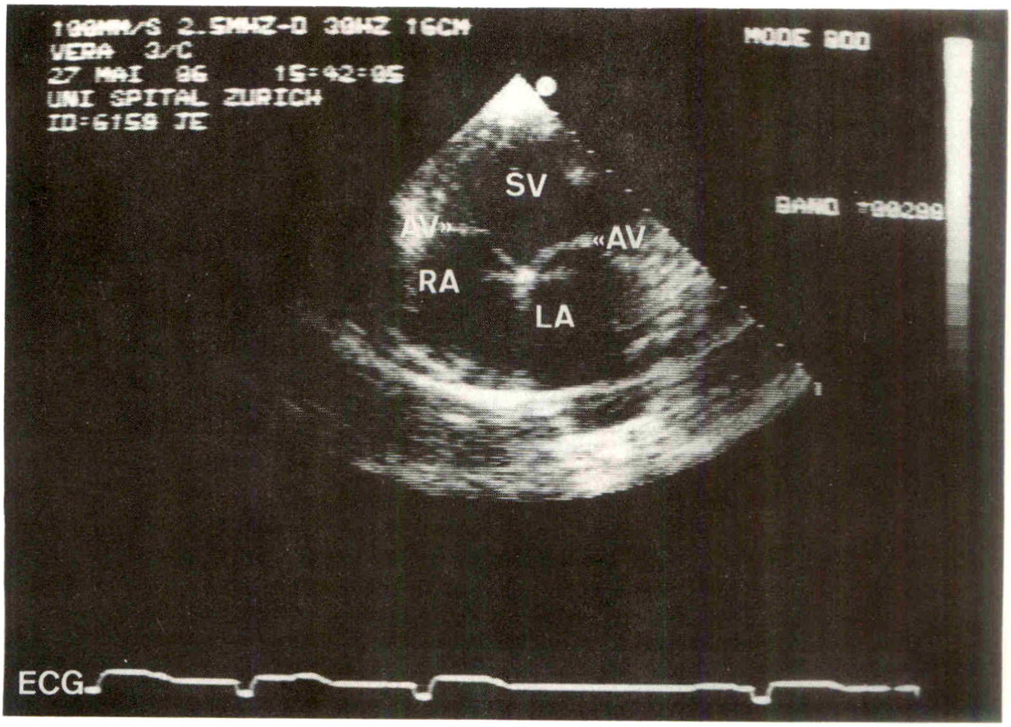

Fig. 1. Cross-sectional apical four-chamber view showing the single ventricle. SV, Single ventricle; RA, right atrium; LA, left atrium; AV, atrio-ventricular valves.

discharged, having no complaints and breast-feeding normally.

Discussion

Pregnancy complicated by congenital and acquired heart disease is found in approximately 1% of patients, with some regional variations; the relative incidence of congenital heart disease has increased in the last years (de Swiet 1984). Of the pregnancies managed between 1970 and 1977 in our department, 20 were complicated, by heart defects, an incidence of 0·18%, and seven (one-third) were congenital cardiac defects (Kunz & Zogg 1980). Atrial septal defect (ASD) and patent ductus arteriosus comprise half of all cases.

A successful pregnancy in a patient with transposition of the great arteries (TGA) and single ventricle is rare. Isolated TGA occurs about once in every 4500 births and in 4% a single ventricle may be involved (Liebman *et al.* 1969). Before the era of heart surgery, most patients with these anomalies never achieved adulthood, although slightly better chances of survival are noted among patients with TGA combined with a single ventricle (Liebman *et al.* 1969). Nowadays, 90% of patients with TGA who have had surgical correction do reach adulthood (Rothlin *et al.* 1983).

Table 1 lists four successful pregnancies in patients with TGA and single ventricle that have been reported previously; two of them occurred in one patient. Three pregnancies have been reported in women with a single ventricle associated with other cardiac anomalies. In the first of these, a healthy infant was born vaginally in the 36th week (Ahmad *et al.* 1981), in the second, fetal death occurred in the 5th month with subsequent maternal death (Mandel & Hirsch 1963), and in the last case, the infant died after premature birth at 25 weeks gestation (Seeds & Cefalo 1977).

TGA with single ventricle is so rare that obstetric care must be derived from the principles applied in other cyanotic heart diseases. During pregnancy, cyanotic cardiac anomalies usually deteriorate by one class of the NYHA classification due to the increase of blood volume and cardiac output (Rothlin 1976). Heart failure and dysrhythmias are the major complications during pregnancy. Oxygenation

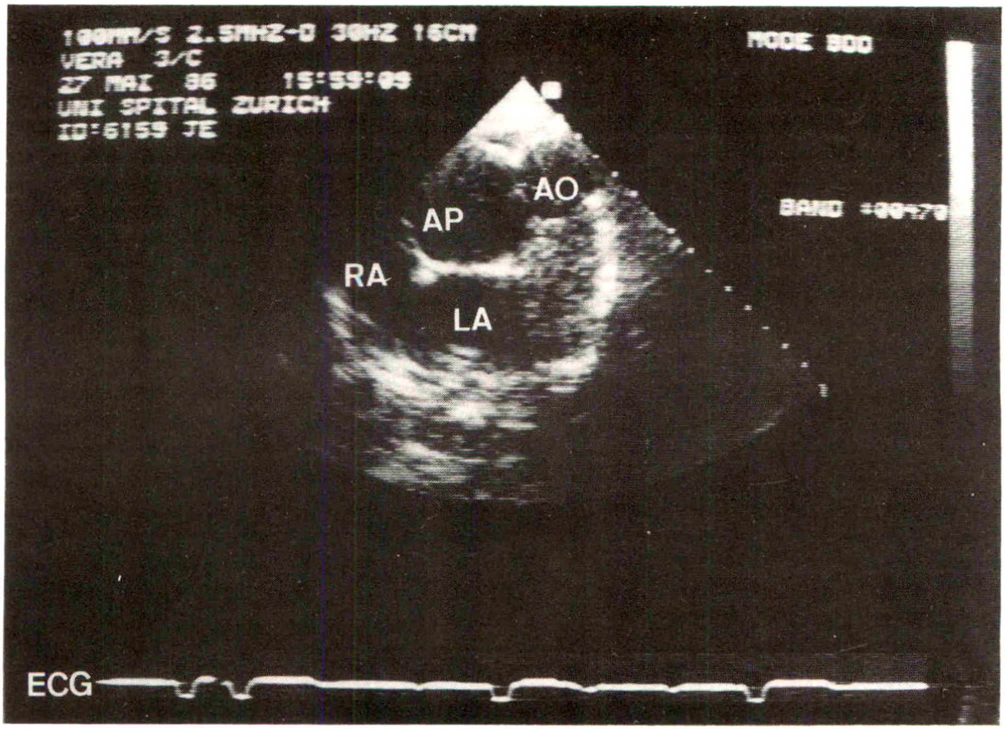

Fig. 2. Cross-sectional left parasternal short axis view showing the transposition of the great arteries. AO, Aorta; AP, pulmonary artery; LA, left atrium; RA, right atrium.

becomes critical when the haematocrit is more than 60% and oxygen saturation less than 80% (Ueland 1978). The most dangerous time is during and after delivery, as several factors may lead to a rapid increase of the pulmonary-to-systemic shunt. This can happen as a result of reduced peripheral resistance (for instance due to anaesthesia), by a diminution of venous return induced by blood loss or vena cava syndrome, or by an increase of pulmonary vascular resistance caused by microthrombosis and hypoxaemia.

Most at risk are women with high pulmonary resistance at the onset of pregnancy (Newfeld *et al.* 1974). Maternal mortality with Eisenmenger syndrome is rated at 27%, with primary pulmonary hypertension 50%, and with Fallot's tetralogy only about 4% (Gleicher *et al.* 1979; Jones & Howitt 1965). The favourable outcome reported in the patients with TGA and single ventricle is probably due to the absence of pulmonary hypertension.

Fetal complications such as intrauterine growth retardation and premature labour are often associated with maternal cyanotic heart disease, and correlate closely with the degree of

Table 1. Case reports of successful pregnancies in women with transposition of the great arteries and single ventricle

Authors	Mode of delivery	Anaesthesia	Gestational age (weeks)	Birthweight (g)
Yuzpe *et al.* (1970)	Caesarean section	General	40	2150 (SGA)
Leibbrandt *et al.* (1982)	Elective caesarean section	Epidural	40	1540 (SGA)
	Elective caesarean section	Epidural	37	1520 (SGA)
Stiller *et al.* (1984)	Elective caesarean section	General (epidural failed)	36	2350 (SGA)
Present case	Elective caesarean section	Epidural	38	2240 (SGA)

SGA, Small for gestational age.

cyanosis. The incidence of cardiac as well as non-cardiac anomalies is increased (Whittemore *et al.* 1982). In a prospective survey of infants born to women with cyanotic heart disease, Whittemore *et al.* (1982) found that 30% of the infants were premature, 67% were small for gestational age, and 87% were under 2500 g. Among patients with TGA and a single ventricle, all infants were small for gestational age and none weighed more than 2500 g. Serial ultrasound measurements are necessary for the early detection of intrauterine growth retardation, and hospitalization is strongly recommended to prevent premature labour.

To compensate for the reduced oxygen saturation, a relatively large placenta in relation to the birthweight has been described (Whittemore *et al.* 1982). The ratio of birthweight to placental weight is normally about 6:1, and in women with cyanotic heart disease this ratio is nearer 5:1. An increase of 2,3-diphosphoglycerate (DPG) in the fetal blood and hence a decrease in oxygen affinity is suggested as an adaptive mechanism within the fetus. The fetal risks and adaptive mechanisms observed in women with cyanotic heart disease are similar to those among pregnant women living at high altitudes (over 2500 m) where a diminution of the arterial P_{O_2} as a result of the lower partial oxygen pressure has been noted (Baumann & Huch 1986).

During delivery continuous maternal and fetal monitoring is vital. Vaginal delivery with epidural analgesia is recommended to diminish exertion and pain (de Swiet 1984; Whittemore *et al.* 1982). However, Table 1 shows that all five pregnancies in the women with TGA and single ventricle were delivered by caesarean section. Epidural anaesthesia proved to be safe, even when general anaesthesia is usually recommended. It is important that unnecessary blood loss is avoided operatively as well as postoperatively. To promote involution of the uterus, oxytocin rather than ergometrin should be administered. Appropriate antibiotic therapy and prophylaxis against thromboembolism is vital. To prevent peripheral venous stasis, support hosiery is strongly recommended throughout pregnancy.

In spite of favourable fetal and maternal outcome in the few reported patients with TGA and single ventricle, one must not overlook the fact that extremely high risk patients were involved, necessitating the co-operation of cardiologists, anaesthesiologists and obstetricians. And because of reduced maternal life expectancy, therapeutic abortion must be discussed and counselling for effective contraception given. Ideally, the pregnancy risk for women with medical problems should be assessed before conception (Hollingsworth *et al.* 1984).

Acknowledgments

We hereby thank P. D. R. Jenni, M.D., M.S.E.E. (Department of Medicine, Medical Polyclinic, University Hospital of Zurich), for the echocardiographic investigation.

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Received 11 July 1986
Accepted 8 September 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol 94, pp. 709–711

Three ectopic pregnancies in one patient. Case report

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Case report

A 21-year-old member of the hospital staff, para 1+0, presented in 1982 with a history of severe lower abdominal pain, vomiting and fainting attacks of 15 h duration after 2 months amenorrhoea. She was pale and had a mass on the left fornix. A clinical diagnosis of haemoperitoneum from a ruptured ectopic pregnancy was made. The haemoglobin was 10·3 g/dl.

At laparotomy, the abdominal cavity was found to contain about 1500 ml of blood and clots. A ruptured left tubal pregnancy was confirmed. The bleeding site, which involved the middle third of the fallopian tube, was clamped, excised and separately ligated (Fig. 1).

The uterus, the right tube and ovaries were grossly normal. There were few pelvic adhesions. Two units of blood were transfused. The postoperative period was uncomplicated and the patient was discharged on the eighth day.

Two years later in 1984 the patient was delivered of a liveborn male infant weighing 4 kg, the pregnancy and delivery were normal and without complications.

One year later the patient was admitted with lower abdominal pain, vomiting and dizziness of 4 days duration. There was no history of amenorrhoea. She looked ill and pale. There was fullness and tenderness over the lower abdomen, but no definite mass could be felt on vaginal examination. Needle aspiration, through the lower abdomen, showed altered blood. A clinical diagnosis of bleeding from a corpus luteum or ectopic pregnancy was made. The haemoglobin was 10 g/dl.

At laparotomy, the abdominal cavity was found to contain about 2 litres of blood and clots from a ruptured ectopic pregnancy situated near the stump of the lateral third of the left fallopian tube.

The points of previous tubal ligation had remained closed and separated by a gap of about 3 cm (Fig. 2). The left ovary contained a corpus luteum.

The ruptured fimbrial end of the tube was excised. Two units of blood were transfused. The postoperative period was uncomplicated and she was discharged on the eighth day.

Ten months later the patient presented again with a history of lower abdominal pain and vaginal bleeding of 5 days duration. Again there was no history of amenorrhoea. No pelvic pathology could be detected on vaginal examination. A diagnosis of dysfunctional uterine bleeding was made and norethisterone acetate, 5 mg twice daily, was given for 5 days. However, the pain and bleeding persisted and when reviewed a week later a definite cystic mass had developed behind and to the right of the uterus. Needle aspiration, through the pouch of Douglas, showed altered blood. A clinical diagnosis of pelvic haemotocele due to a leaking ectopic pregnancy was made. The haemoglobin was 13·1 g/dl.

At laparotomy, a ruptured right ampullary tubal pregnancy, with an adjacent large pelvic haematocele extending into the pouch of Douglas and the right parametrium, was found (Fig. 3). Total right salpingectomy was performed and haematocele evacuated. The isthmus of the left fallopian tube which was distended with blood was excised. The uterus and both ovaries were normal. The postoperative period was uneventful and the patient was discharged on the ninth day.

Discussion

Ectopic pregnancy is the second most common gynaecological emergency at the Royal Victoria Hospital in Banjul; it reflects the high incidence of tubal damage secondary to pelvic infection,

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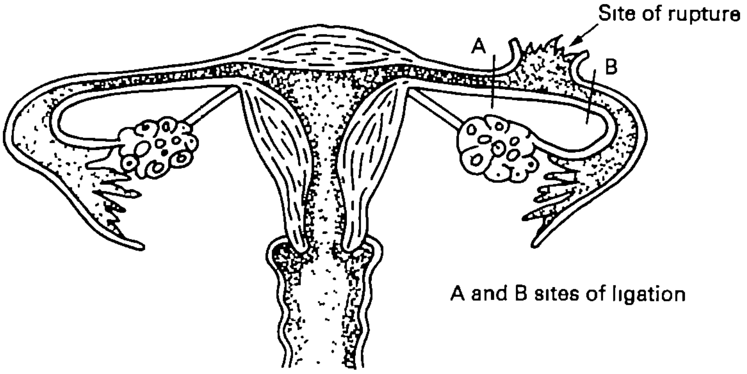

Fig. 1. Diagrammatic representation of site of rupture in first ectopic pregnancy.

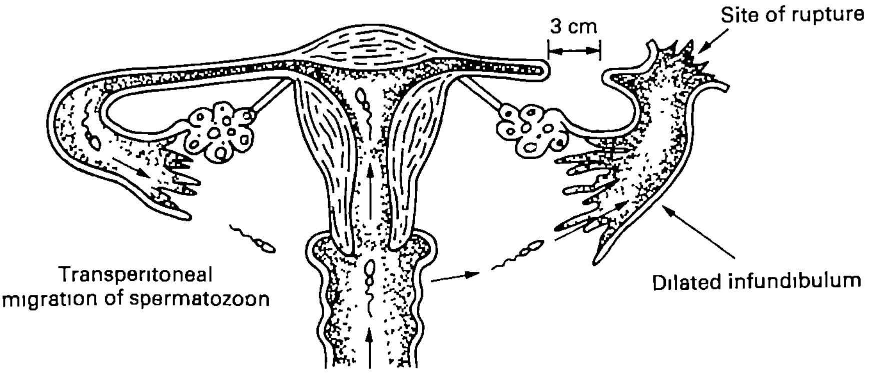

Fig. 2. Diagrammatic representation of site of rupture in second ectopic pregnancy

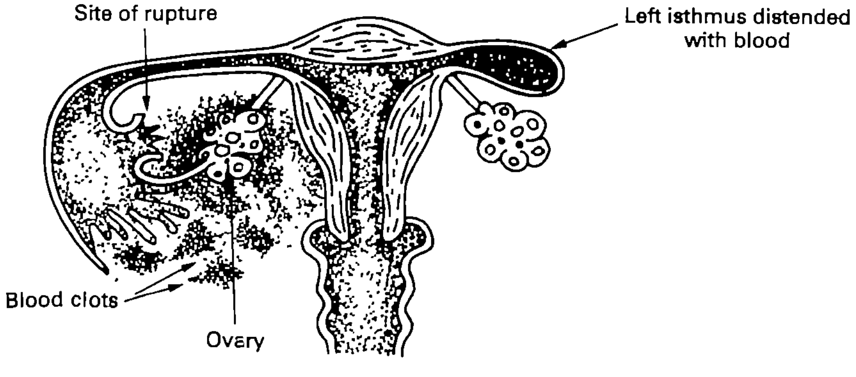

Fig. 3. Diagrammatic representation of site of rupture of third ectopic pregnancy

but three ectopic pregnancies (and one normal delivery) in one patient, all diagnosed and managed by one person, must be a rare occurrence.

General ill health with lower abdominal pain and pelvic tenderness with or without a pelvic mass were the most consistent features of all three ectopic pregnancies. Anaemia was not a feature and a history of amenorrhoea was obtained on only one occasion, demonstrating that symptoms of ectopic pregnancy can start before or during the onset of an expected period. Bimanually directed needle aspiration of 'altered' blood from an area of fullness or cystic mass was helpful in confirming the diagnosis but a false negative or false positive aspirate can occur.

Left partial salpingectomy was performed for the first ectopic pregnancy because it was the easiest and safest thing to do at the time. An ectopic pregnancy in the remains of the left tube was unexpected. With the points of the previous tubal ligation closed, it is almost certain that the sperm, gaining access to the pelvic cavity through the patent right tube, had migrated and fertilized an ovum sucked into the infundibulum of the left tube. This mechanism is likely to occur more often in future where resection of the middle of the tube rather than salpingectomy is performed.

Acknowledgment

The illustrations were prepared by Trevor Towle, Department of Medical and Health, Banjul.

Received 14 April 1986
Accepted 19 June 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp 712–715

Vasa praevia—report of three cases and review of literature

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Case reports

Patient 1

A 32-year-old woman with one previous successful pregnancy had an ultrasound scan at about 16 weeks gestation which confirmed her dates and revealed a placenta covering the os. She was admitted at 27 weeks gestation with painless vaginal bleeding which settled spontaneously. An ultrasound scan revealed a minor degree of placenta praevia. A repeat scan at 34 weeks gestation showed a normally situated placenta. Because of the antepartum haemorrhage, induction of labour was planned for 40 weeks gestation.

At amniotomy there was a brisk, fresh blood loss per vaginam of about 100–200 ml and the fetal heart ceased to be detectable within 2 min. Uterine activity was stimulated with oxytocin. A stillborn female infant weighing 3345 g was born spontaneously. Fetal death was due to exsanguination from ruptured vasa praevia.

Patient 2

This patient was pregnant for the fourth time at the age of 26 years. She had one living child and had had two miscarriages. The antenatal period was uneventful.

She was admitted in spontaneous labour at 40 weeks gestation. The fetal heart was not detectable. The cervix was 6–7 cm dilated and she was draining blood-stained amniotic fluid. A stillborn female infant weighing 2980 g was born spontaneously, 17 min later. Fetal death was due to exsanguination from ruptured vasa praevia.

Patient 3

This 22-year-old primigravida had an uneventful antenatal period and was admitted at about 40 weeks gestation with mild uterine contractions and draining clear amniotic fluid. The cervix was partially effaced and 2 cm dilated. The presentation was cephalic. An hour after admission slight fresh vaginal bleeding was accompanied by deep early decelerations (fetal heart rate dropping from 150 beats/min to 60 beats/min) on the cardiotocograph, recorded via an abdominal transducer. A provisional diagnosis of placental abruption was made and she was delivered by caesarean section of a live female infant weighing 3033 g, with Apgar scores of 6 and 9 at 1 and 5 min, respectively. The baby did not require any active management and thrived. Examination of the placenta revealed a ruptured velamentous vessel, there was no retroplacental clot.

Discussion

As perinatal mortality rates continue to decline, the rarer causes of perinatal death assume increased relative importance. Vasa praevia is rarely encountered and yet undoubtedly more common than a review of the literature would suggest. According to Douglas & Lloyd (1981) only about 120 cases have been reported since Lobstein (1801) first described vasa praevia. Vago & Caspi (1962) found a prevalance of 1 in 2761 deliveries between 1950 and 1960 in their hospital whereas Quek & Tan (1972) reported a prevalence of 1 in 5000 deliveries over a 40-month period. Velamentous insertion of the cord, which is a prerequisite of vasa praevia, occurs in 0·2–1·2% of singleton pregnancies and in over 10% of multiple pregnancies. In the series reported by Quek & Tan (1972) the likeli-

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hood of vasa praevia occurring in patients with velamentous cord insertion was about 1 in 50.

Pent (1979) defined vasa praevia as 'an anomaly of the insertion of the umbilical cord into the placenta in which the umbilical vessels traverse the lower uterine segment and present in advance of the fetal presenting part'.

We propose the following definition: 'Vasa praevia is a condition in which the velamentous vessels traverse the lower uterine segment and present in advance of the fetal presenting part'.

Modes of presentation

Our patients illustrate three of the different modes of presentation of vasa praevia.

Vessel rupture at amniotomy. This is the classical textbook presentation of vasa praevia and is demonstrated by our first patient. Vago & Caspi (1962) and Antoine *et al.* (1982) have also reported similar cases.

Vessel rupture before rupture of membranes. The patient may present with antepartum or intrapartum bleeding or, as in our second patient, draining blood stained amniotic fluid. Vago & Caspi (1962), Pallewala (1974) and Douglas & Lloyd (1981) have also reported cases presenting by this mode.

Vessel rupture after rupture of membranes. The bleeding starts some time after the membranes rupture. This is due to the progressive extension of the tear in the amnion to eventually involve the velamentous vessels. Our third patient presented in this manner. Vago & Caspi (1962), Carp *et al.* (1978) and Pent (1979) have reported vessel rupture after rupture of the membranes.

Vessel compression. Compression of vessels may lead to early or variable decelerations on the cardiotocograph as in the patients reported by Naftolin & Mishell (1965), Carp *et al.* (1978) and Tejani *et al.* (1979).

Vessels palpable on vaginal examination. The vessels have been described as being thin, pulseless and relatively immobile. Paulino (1970), Quek & Tan (1972), Pahuja (1976) and Carp *et al.* (1979) have described cases presenting by this mode.

Diagnosis

Timely diagnosis of vasa praevia poses a real problem. A high index of suspicion is our best diagnostic aid. The condition of vasa praevia should be kept in mind whenever antepartum and intrapartum haemorrhage occurs, especially if there are fetal heart rate (FHR) irregularities with scanty vaginal bleeding; if placenta praevia and abruption are unlikely or if there is a multiple gestation. The diagnosis may be established in several ways as follows.

Palpation of the vessels and amnioscopy. The main difficulty is in differentiating between velamentous vessels and an umbilical cord. The former can be identified by their smaller diameter, lack of mobility and lack of free space around them. Benchiser (1831) and Quek & Tan (1972) noted that the pulseless vessels could be felt on vaginal examination. Carp *et al.* (1979) actually noticed a vessel bleeding at the vulva and ligated it after collecting a blood sample, this was subsequently found to be a velamentous vessel and in another triplet pregnancy they palpated a pulsatile velamentous vessel. Barham (1968) recommended amnioscopy to view the vessels before amniotomy; when FHR irregularities developed and if unexplained intrapartum bleeding occurred. Amnioscopy also facilitates the collection of a blood sample for chemical testing.

Tests for the presence of fetal haemoglobin. A smear of vaginal blood may be stained with the Wright stain to identify normoblasts and nucleated erythrocyctes which are present specifically in fetal blood. Several chemical tests have been described, all based on the fact that fetal haemoglobin is more resistant than maternal haemoglobin to denaturation by alkali (Apt & Downey 1955; Kleihauer *et al.* 1957; Mitchell *et al.* 1957; Chamberlain & Foster 1970; Ogita *et al.* 1976; Loendersloot 1979). For the Apt test, which seems to be the most frequently used, 2–3 ml of the bloody fluid are mixed with an equal quantity of water and centrifuged for 2 min at 2000 rev/min. Five parts of the clear supernatant are mixed with one part of 1% NaOH and the colour change is observed after 2 min. Maternal blood changes from pink to yellow brown whereas fetal blood remains pink.

The Ogita test is simpler because a centrifuge is not required and Loendersloot (1979) described an even simpler test which just needs two test tubes containing 10 ml of 0·1 N K O H. A few drops of vaginal blood are added to one 10 ml sample and the same amount of maternal blood is added to the second sample. If the vaginal blood contains no fetal erythrocytes both samples will be a yellow brown colour within 20 s but if fetal haemoglobin is present the first sample will remain pink. As in the Apt and Ogita tests, maternal sickle cell disease and thalassaemia may give misleading results.

Douglas & Lloyd (1981) used haemoglobin electrophoresis to diagnose vasa praevia antenatally because fetal and maternal haemoglobins have different electrophoretic mobilities. The procedure uses 0·5 ml of clotted or unclotted blood, takes 1 h approximately and should be virtually 100% reliable.

Cardiotocography. This can only be considered as a useful adjunct and does not have a diagnostic role. Early and variable decelerations due to vessel compression have been described by Naftolin & Mishell (1965) and Tejani *et al.* (1979). Antoine *et al.* (1982) and Douglas & Lloyd (1981) found sinusoidal fetal heart rate pattern in infants who were severely anaemic at birth.

Ultrasound. As obstetric ultrasound techniques improve it should be possible to diagnose velamentous cord insertion and vasa praevia by following the umbilical artery and vein from the fetal end of the cord. Pent (1979) has mentioned the possibility of distinguishing the umbilical artery from the vein by ultrasound.

Management

If the fetus is dead vaginal delivery is appropriate. If the fetus is alive delivery must be by the quickest and least traumatic route as soon as vasa praevia is diagnosed; this is usually by caesarean section. The infant may need immediate transfusion.

Prognosis

Vasa praevia is unique in that it is the only condition in which there is a high fetal mortality and morbidity in the complete absence of maternal mortality.

The fetal mortality is 75–100% in patients with vessel rupture and 50–60% in those with cord compression (Naftolin & Mishell 1965). Nine twin pregnancies with vasa praevia have been reported to date, the mortality for twin 1 was 100% while for twin 2 it was about 55%. The duration of bleeding does not appear to affect the outcome. The patient reported by Douglas & Lloyd (1981) had three episodes of antepartum haemorrhage from 35 weeks onwards, the diagnosis was established by haemoglobin electrophoresis at the third episode (approximately 37 weeks gestation). The baby was born by caesarean section, required immediate transfusion and survived. The series reported by Vago & Caspi (1962) also illustrates this point. It is likely that in some cases the tear in the vessel is sealed off by a clot.

In conclusion we consider that because vasa praevia is so uncommon, a high index of suspicion and familiarity with the modes of presentation is essential if the condition is to be diagnosed early enough. An increasing use of chemical testing for fetal haemoglobin and amnioscopy could result in saving an infant who otherwise would have been another stillbirth statistic. Every labour ward should have facilities for detection of fetal haemoglobin, the test described by Loendersloot (1979) appears to be quick, simple and cheap.

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Received 12 August 1986
Accepted 10 September 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol. 94, pp. 716–718

Symphysiotomy for vaginal breech delivery: two case reports

JOHN A. D. SPENCER

Case reports

Patient 1

A 30-year-old primigravida, 1·67 m tall, was seen at term with an extended breech presentation after an uneventful pregnancy. Ultrasound measurements gave an estimated fetal weight of 3 kg and antero-posterior measurements on a lateral pelvic X-ray were inlet 12·4 cm, mid-cavity 13·1 cm and outlet 13·1 cm. She began labour spontaneously and was transferred to the delivery suite where the cervical dilatation was found to be 6 cm. The fetal membranes were ruptured and 30 min later she requested epidural analgesia. The cervix was then 9 cm dilated and before the epidural could be given she started pushing. Following an episiotomy the breech and legs were born spontaneously and the arms were born uneventfully using Lövset's manoeuvre. No further progress occurred as the head failed to descend further into the pelvis. Despite continued suprapubic pressure the Mauriceau–Smellie–Veit procedure was unsuccessful as was an attempt to bring the head down with forceps. A subcutaneous symphysiotomy was therefore performed after infiltrating the mons pubis with 1% lignocaine and inserting a catheter to displace the urethra from the midline. The superior and anterior fibres of the symphysis pubis were divided using a disposable scalpel and the thighs were slowly abducted until the fetal head descended into the pelvis. Delivery was expedited using forceps. The symphysis had separated approximately 2 cm and the interval between delivery of the umbilicus and the head had been 11 min.

The female infant weighed 3·48 kg and was white and limp with a bradycardia. She was intubated immediately by the attendent paediatrician. The heart rate recovered well and the baby was pink after 3 min of intermittent positive pressure ventilation in 100% oxygen. The first gasp was at 4 min of age and spontaneous respiration was established by 15 min; she was extubated at 20 min. The Apgar scores were 1,4,6 and 8 at 1,5,10 and 15 min respectively and the umbilical cord vein pH was 7·09 with a base deficit of 20 mmol/l. By 15 min of age an umbilical vein catheter had been inserted and the pH had improved to 7·17. The baby was nursed in the neonatal special care unit and was noted to have mild cerebral irritability for 24 h after which there were no further problems.

The third stage of labour was uneventful as was repair of the episiotomy and suprapubic stab incision. The mother's legs were then strapped together for 24 h and she was nursed on her side for 3 days. She was fitted with a pelvic binder by the physiotherapy department who supervised her gradual mobilization over the subsequent 8 days. She initially used a walking frame but by the time of discharge was walking unaided without discomfort. Postpartum pelvimetry showed no change in the pelvic measurements and revealed an interspinous measurement of 9·3 cm. Both mother and infant were discharged on day 13 and were well at follow-up 4 weeks later. The infant subsequently exhibited a slight delay in motor development but this had caught up by 18 months. She was discharged from follow-up at 2 years of age.

Patient 2

A 33-year-old primigravida, 1·60 m tall, had an ultrasound scan at 38 weeks to confirm an

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extended breech presentation. Fetal size was considered average and pelvimetry was not performed. Three days later she was admitted in spontaneous labour with ruptured membranes and a cervical dilatation of 8 cm. One hour later full dilatation was confirmed when she wanted to push. One percent lignocaine was used for perineal infiltration and a pudendal block and, following an episiotomy, the breech and legs were born spontaneously. The feet were born by flexing the knees but progress ceased at the level of the lower edge of the shoulder blades. Gentle traction on the breech together with maternal effort was unsuccessful in achieving delivery of the shoulders. Examination confirmed extended arms which were probably locked behind the head preventing further descent. Two attempts to bring down an arm after rotation of the fetal trunk in both directions were unsuccessful and so the decision to perform a subcutaneous symphysiotomy was made. The preparations were as described in our first patient and the legs were supported by lithotomy poles. Once the superior and anterior fibres of the symphysis had been divided the symphysis parted suddenly and the fetal shoulders and head dropped into the pelvis. Lövset's manoeuvre was used to deliver the fetal arms and the Burns–Marshall technique was used to deliver the head without any further difficulty. The symphysis had parted by 4 cm and the interval between delivery of umbilicus and head was 4 min.

The female infant weighed 2·525 kg and was white and limp. In view of a persisting bradycardia she was intubated at 30 s of age. Regular respiratory efforts were present after 2 min of intermittent positive pressure ventilation and she was extubated at 3 min. The Apgar scores were 1,8 and 10 at 1,5 and 10 min respectively. The umbilical cord artery blood had a pH 7·05, $P\text{co}_2$ 61 mmHg, $P\text{o}_2$ 12 mmHg and a base deficit of 16 mmol/l whilst the umbilical vein blood had a pH 7·37, $P\text{co}_2$ 24, $P\text{o}_2$ 38 and a base deficit of 9·5 mmol/l. The infant was observed on the neonatal unit but as there were no problems she was returned to the ward the next day.

Post delivery management of the mother was the same as in our first patient except that general anaethesia was necessary for a manual removal of the placenta. After repair of the episiotomy the mother's legs were carefully laid straight on the delivery bed and strapped together at the knees and ankles. In view of the large separation of the symphysis pubis two nylon sutures were used to stabilize the joint. The vertical incision in the skin over the public symphysis was enlarged to 3 cm and the nylon sutures were inserted into the anterior periosteum on either side of the symphysis and tied across the front of the joint. Interrupted silk sutures were used to close the skin incision over the pubis and vacuum drainage of the deep tissue space anterior to the symphysis was maintained for 24 h. Mobilization was again supervised by the physiotherapy department and she was walking unaided by the 10th day. Postnatal pelvimetry showed that the inlet was 10·8 cm with a midcavity of 14·2 cm and an outlet of 12·5 cm. The interspinous measurement was 13·6 cm. She was discharged with her baby on day 13. When seen at follow-up 6 weeks later she had a mild degree of discomfort in both sacro-iliac joints.

Comment

The operation of symphysiotomy has been advocated as an alternative to caesarean section for the delivery of women in whom there appears to be a mild degree of cephalopelvic disproportion. It was first performed in Paris by Sigault in 1768 and continues to be performed in some parts of the world (Gebbie 1982). Its lack of popularity in the UK, as in America and Scandanavia, seems to have started in the 19th century with the Protestant philosophy of non-interference for fetal problems by methods which would in any way jeopardize the mother's health (Gebbie 1982). However, many Catholic countries in Europe, including Ireland, continued to use the procedure in the presence of cephalopelvic disproportion rather than resort to early induction of labour or embryotomy and forceps delivery (Spain 1949). Caesarean section is now the prefered method of dealing with the problem of cephalopelvic disproportion in the UK but symphysiotomy has been shown to be safer in less developed countries (Campbell 1986). Shoulder dystocia has also been described as an indication for emergency symphysiotomy (Hartfield 1986).

The operation of symphysiotomy does not require a general anaesthetic and is a simple procedure with local analgesia (Hartfield 1973). Early descriptions of the procedure stressed the safety of a solid-bladed scalpel to perform the operation (Seedat & Crichton 1962) but Gebbie (1982) points out that a detachable blade is adequate if used with care. In both our patients the procedure was performed with a disposible plastic scalpel. Adequate support of the mother's legs is an important aspect of the technique. Zarate (1955) recommended that the legs be held by two assistants at a 90° angle and slowly parted until separation is sufficient to overcome the obstruction (Browne 1968). Alternatively, the legs may be supported in lithotomy poles and the thighs prevented from abducting more than 90° by a bandage wound several times between the knees (Gebbie 1982). It is important to prevent sudden separation of the symphysis as this is likely to result in excessive strain of the sacroiliac joints.

A Lancet Editorial (1974) suggested that the combination of symphysiotomy and vacuum extraction should be known by those 'going beyond the reaches of the safer, well-equipped labour ward' but Hartfield (1973) recommended that symphsiotomy be included in the curricula of all teaching hospitals. Such a suggestion seems justified by the successful outcome of the two cases reported here in which an emergency symphysiotomy was performed for unexpected pelvic entrapment of the after-coming head during planned vaginal breech delivery, a use described by Seedat & Crichton (1962), Browne (1968) and Gebbie (1982). Neonatal survival relates to the time delay from head retention to delivery whereas maternal complications relate to the speed with which the operation is performed (Gebbie 1982). Most easy breech deliveries follow rapid descent of the presenting part during the first stage and Gebbie (1982) recommends timely symphysiotomy when descent of the breech in the early part of the first stage of labour has been slow. Both our patients had a rapid first stage of labour with no indication of a possible problem with delivery, and they reinforce the view that breech delivery should not be undertaken without the ability to perform an emergency symphysiotomy (Browne 1967).

Acknowledgments

I thank Mr M D. Gillmer and Mr I. Z. Mackenzie for permission to report these two cases, Mr B. Castle who managed the first case and Professor A. Browne for his comments on the manuscript.

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Received 21 August 1986
Accepted 19 November 1986

British Journal of Obstetrics and Gynaecology
July 1987, Vol 94, pp 719–720

BOOK REVIEWS

Drug Therapy During Pregnancy edited by Tom K. A. B. Eskes & Mieczyslaw Finster. Butterworths, Sevenoaks, 1985, 230 pages with figures and tables, £35.00

This book is edited by the promising combination of a Dutch obstetrician and an anaesthetist from the United States, both eminent in their respective specialties, and with particular expertise in the field of drugs in pregnancy. The majority of authors are from the United States and Holland with contributions also from Switzerland, Belgium and the UK. The content is varied and interesting, well referenced and indexed.

A brief introduction from the Dutch team deals with the epidemiology of drug use in pregnancy, which is followed by a competent and helpful chapter on pharmacokinetics from Beatrice Krauer. In the section on materno-fetal equilibration, however, she rather oddly omits the effect of differential protein binding, a subject on which she herself is an expert (could this be an editorial cut?). Teratogenesis and developmental toxicology are covered in two widely separated chapters, and also in sundry other places in connection with particular classes of drugs. The chapter on hypertension in pregnancy is thorough, but contains an incomprehensible figure on page 54, an odd statement that nitroprusside produces more venodilatation than other vasodilators and a section on reserpine written in the present tense but borne out, as would be expected, by references more than 30 years old. The chapter on anti-epileptic drugs has an orderly presentation but might mislead the reader about diazepam metabolism, protein binding and valproate interactions

The chapter on anaesthesia in pregnancy contains a major section headed 'Perinatal Pharmacology' which includes placental transfer, and might better have been covered by Dr Krauer. The same old inapplicable formula is trotted out to describe placental transfer. The chapter covering uterine stimulation is practical. The next, relating to beta-adrenergic drugs, is concise but omits advice on dosage. Other chapters deal most efficiently with hormone therapy, with non-steroidal anti-inflammatory drugs and with the effect of drugs on fetal heart patterns.

I was rather disappointed to find no chapter on the knotty problem of anticoagulation in pregnancy. With this exception, I think the editors have selected their topics well, and have produced a book which is thorough without being unreadably long. The production is good, though I found that I lost my place rather easily between the long lines of type.

Felicity Reynolds

The Developmental Field Concept edited by John M. Opitz. Alan R. Liss, New York, 1986, 476 pages with figures and tables, £44.00

This book contains two additions of the *American Journal of Medical Genetics,* bound as one volume. The common theme is the developmental field concept and this is reinforced by editorial comments from Dr Opitz, who is one of the originators and main proponents of this concept. Opitz explains the concept in the following way: 'Given that a specific malformation is demonstrated to occur as two or more *causally different* traits, then a developmental field defect has been defined in the sense of a dysmorphogenetically reactive unit, i.e., a set of embryonic primordia that react *identically* to *different* causes. It then follows that these primordia must also constitute a morphogenetically reactive unit under normal circumstances.' In other words, if a developmental abnormality can be shown to be caused by two or more different factors, it is likely that there is some underlying, common path of development. Opitz provides a very valuable historical perspective for this idea, reviewing the ideas of 19th century embryologists and anatomists.

The bulk of the book is taken up by individual scientific papers on varying topics, with the rather loose connection that they possibly illustrate developmental field defects. Thus they range from epidemiological studies on hypospadias, renal agenesis, imperforate anus and neural tube defect to individual case reports on a variety of single gene and sporadic syndromes.

This book will be fascinating for the clinical geneticist and paediatric pathologists, but it should be already available to them if they subscribe to the *American Journal of Medical Genetics,* and as most large medical libraries will also have this Journal, I can't see that there will be a market for this worthy text.

R. M. Winter

Obstetric Ultrasound: How Why and When by Patricia Chudleigh & J. Malcolm Pearce. Churchill Livingstone, Edinburgh, 1986, 194 pages with figures and tables, £14.95

There has existed a need for an up-to-date, reasonably priced, practical guide to obstetric ultrasound. This excellent book satisfies that need. Its subject matter ranges from measurement of Graafian follicle before ovulation to identification of retained products of conception during the puerperium. In between, all established applications of obstetric ultrasound are discussed with clarity and from a sensible practical standpoint achieved only by long experience. The sections on fetal anatomy and abnormality are especially good. Throughout, the uses of ultrasound are placed against their relevant clinical background and this is important because the book will appeal to a much wider readership than just obstetricians. The illustrations are clear and the reproduction of ultrasonograms is of high quality. The text has been deliberately written in a no-nonsense style, without references, which hides controversies but other, larger, books exist to debate the pros and cons of the finer details. A better practical guide does not exist and this will, I predict, become the standard manual for all learning the art of obstetric ultrasonography.

Jim Neilson

Books received some of which may be reviewed at a later date

Handbook of Neonatology Second edition by Rita G. Harper & Jing Ja Yoon. Year Book Medical Publishers, Inc., Chicago, London, 1986, 718 pages with figures and tables, £38.50

Pathology of the Vulva and Vagina (Contemporary Issues in Surgical Pathology, Vol 9) edited by Edward J. Wilkinson. Churchill Livingstone, New York, Edinburgh, 1987, 340 pages with figures and tables, £45.00

Urinary Tract Infections (Series in Clinical Epidemiology) by John R. Dalton & Erick J. Bergquist. Croom Helm, London & Sydney, 1987, 266 pages, £29.95

Obstetrics: Normal & Problem Pregnancies edited by Steven G. Gabbe, Jennifer R. Niebyl & Joe Leigh Simpson. Churchill Livingstone, New York, 1986, 1148 pages with figures and tables, £60

Handbook for Prescribing Medications During Pregnancy Second edition edited by Richard L. Berkowitz, Donald R. Coustan & Tara K. Mochizuki. Little Brown & Company, Boston/Toronto, 406 pages, £14.15

Spontaneous and Recurrent Abortion edited by Michael J. Bennett & Keith Edmonds. Blackwell Scientific Publications, Oxford, 1987, 248 pages with figures and tables, £29.50

Inflammation—Mediators and Mechanisms—British Medical Bulletin, Vol 43, No. 2 Scientific Editor D. A. Willoughby. Published for the British Council by Churchill Livingstone, London, 1987, 247–447 pages with figures and tables, £20 (UK) £21.25/$40 (overseas)

Clinical Pocket Manual: Ob/Gyn Care edited by Katherine W. Carey & Kathy E. Goldberg. Nursing 87 Books, Springhouse Corporation, Springhouse Pennsylvania, 1987, 187 pages with figures and tables, no price given

Diagnostic Picture Tests in Obstetrics and Gynaecology by H. Joyce, J. F. Patrick, G. D. Reid, F. L. Wilcox & V. R. Tindall. Wolfe Medical Publications Ltd., Ipswich, 1987, 139 pages fully illustrated with colour plates, £6.50

Induced Abortion. A World Review 1986 Sixth edition by Christopher Tietze & Stanley K. Henshaw. Obtainable from The Alan Guttmaher Institute, 111 Fifth Avenue, New York, NY 10003, USA, $10

Atlas of Fetal Sectional Anatomy With Ultrasound and Magnetic Resonance Imaging by G. Isaacson, M. C. Mintz & E. S. Crelin. Springer-Verlag, Berlin-Heidelberg, New York, 184 pages with 278 figures, DM 228

Compedio Di Isterosalpingografia by Aurelio Tetti & Cesare Tetti. Edizioni Minerva Medica S.p.A., Corso Bramante 83/85, Torino, 1987, 92 pages fully illustrated, no price given

Paediatric and Perinatal Epidemiology

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B.-J. Hackelöer, V. Duda, G. Lauth, Marburg

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This monograph discusses in depth ultrasound mammography, one of the leading methods in breast examination today. Comparisons with competing diagnostic techniques, such as thermography and especially radiography, are included. Images from realtime scanners and immersion scanners highlight the fascinating illustrative material.

C. Ammeuer, Paris

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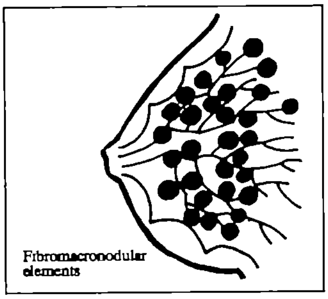

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Editors S. Brünner, University of Copenhagen, B. Langfeldt, University of Aarhus

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C. Ray, Uxbridge, M. Baum, London

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1985. VIII, 133 pages. (Contributions to Psychology and Medicine) Hard cover DM 102,–
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Women with Cancer

Psychological Perspectives

Editor: B. L. Andersen, The University of Iowa

1986. XVIII, 326 pages. (Contributions to Psychology and Medicine). Hard cover DM 118,–
ISBN 3-540-96360-X

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Altman, D G , Gore, S M., Gardner, M. J. & Pocock, S J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

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Trudinger, B J , Lewis, P J & Petit, B (1979) Fetal breathing in intrauterine growth retardation *Br J Obstet Gynaecol* **86**, 432-436

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Vol 94 No 7 July 1987

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British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten

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Published on behalf of the
Royal College of Obstetricians and Gynaecologists
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BJOGAS 94(8) 721–832 1987 ISSN 0306-5456

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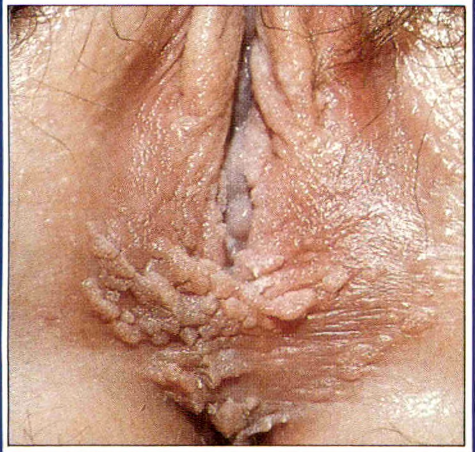

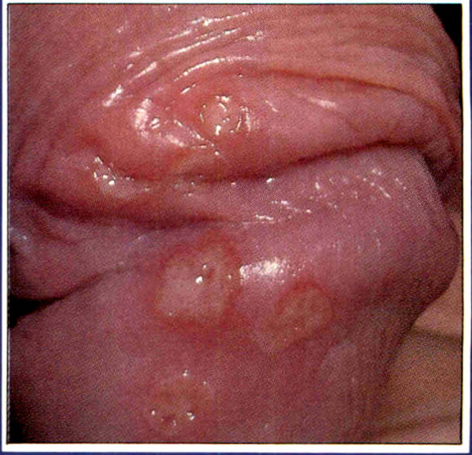

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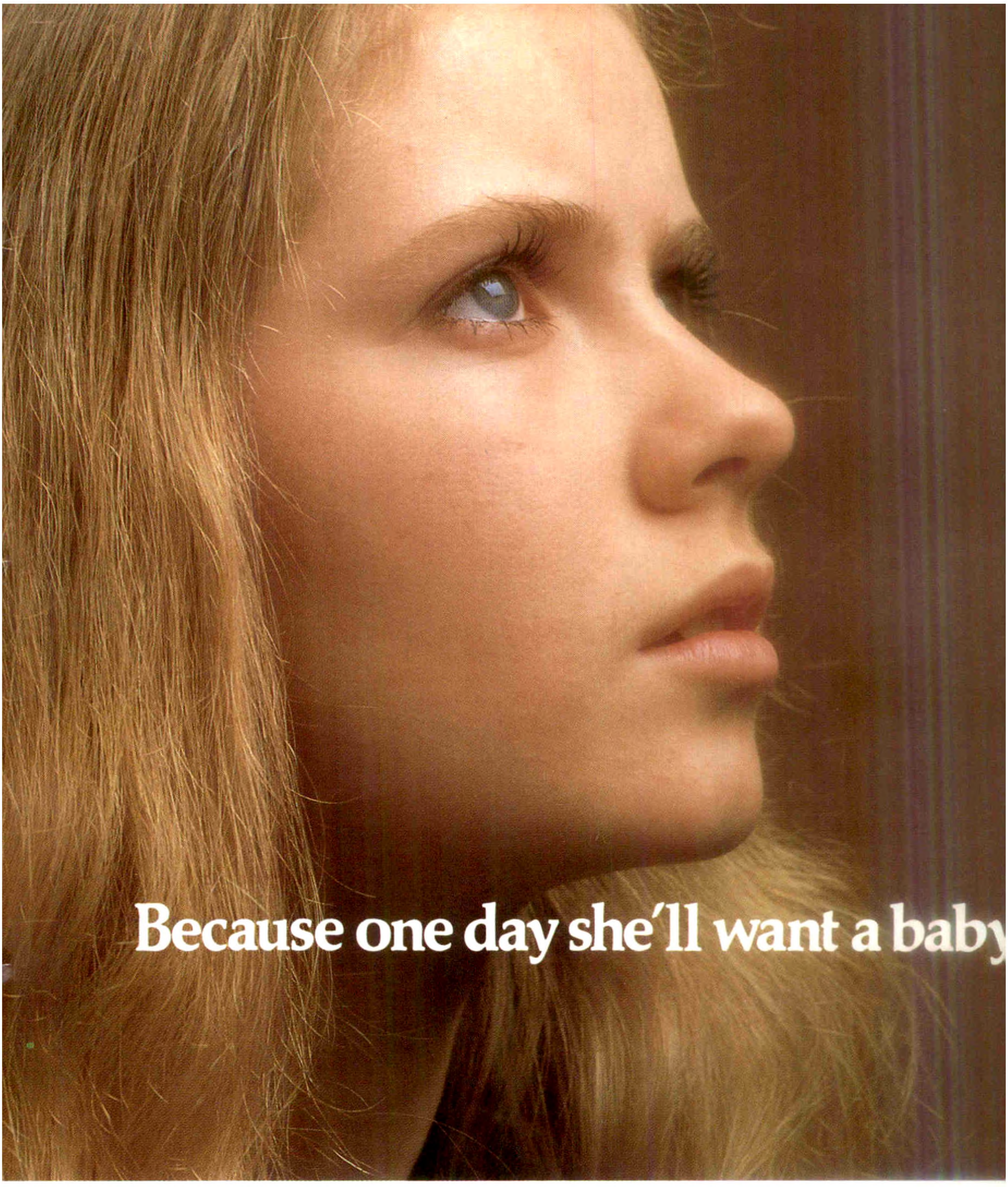
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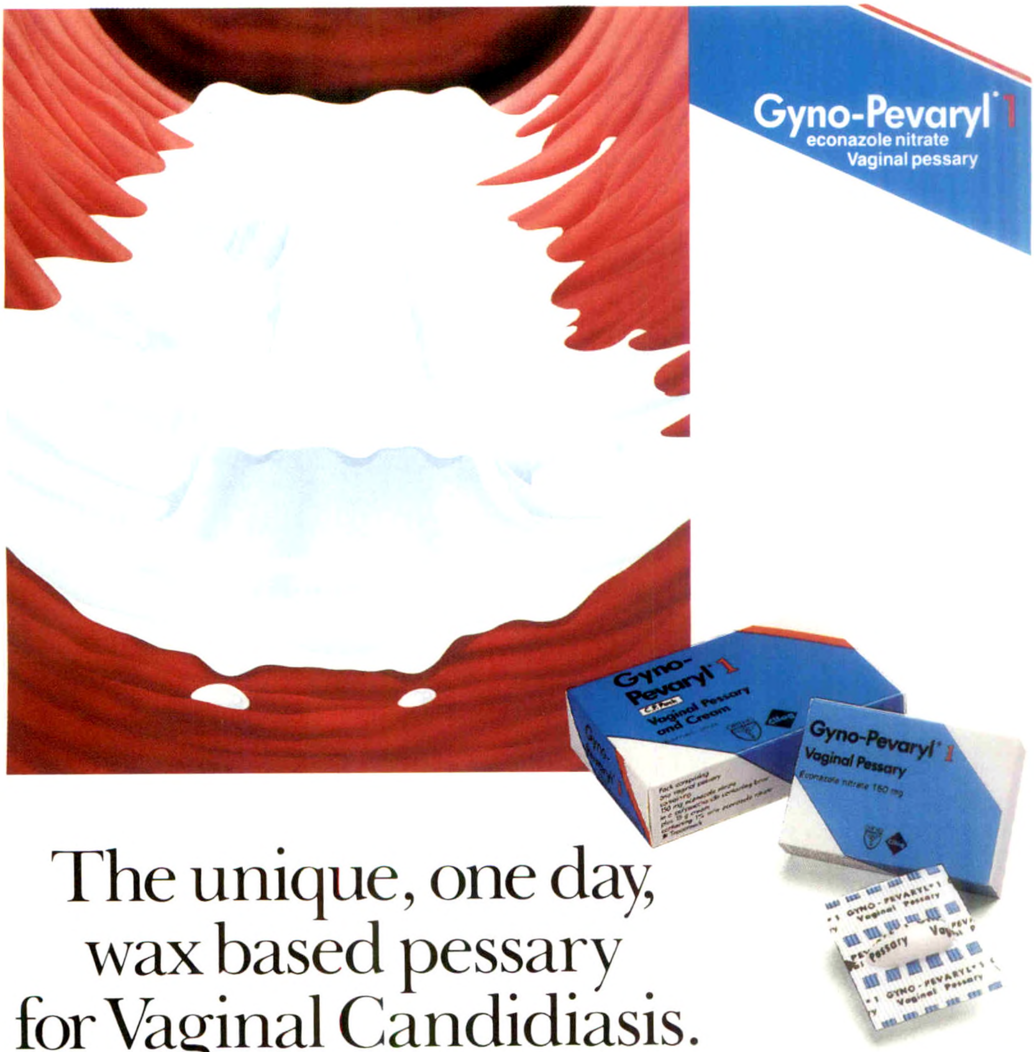
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References

1 Franks, S et al - J Endocrinol, (1985) 104 p 34 Abst 41
2 Yen, S S C et al J Clin Endocrinol, Metab (1970) 30, pp 435-442
3 Data on file
4 Ginsburg, J et al "Ovulation and Pregnancy after pure FSH Therapy in Sclerocystic Ovarian Change" XIth World Congress of Gynaecology & Obstetrics
5 Braendle, W et al "Advances in Diagnosis and Treatment of Infertility" Ed V Insler and G Bettendorf (1981) pp 33-41, Elsevier, North Holland
6 Gocial, B Wu, C H et al Society for Gynaecological Examination 31st Annual Meeting, San Francisco (21-24 March 1984) Abstract No 279, pp 164

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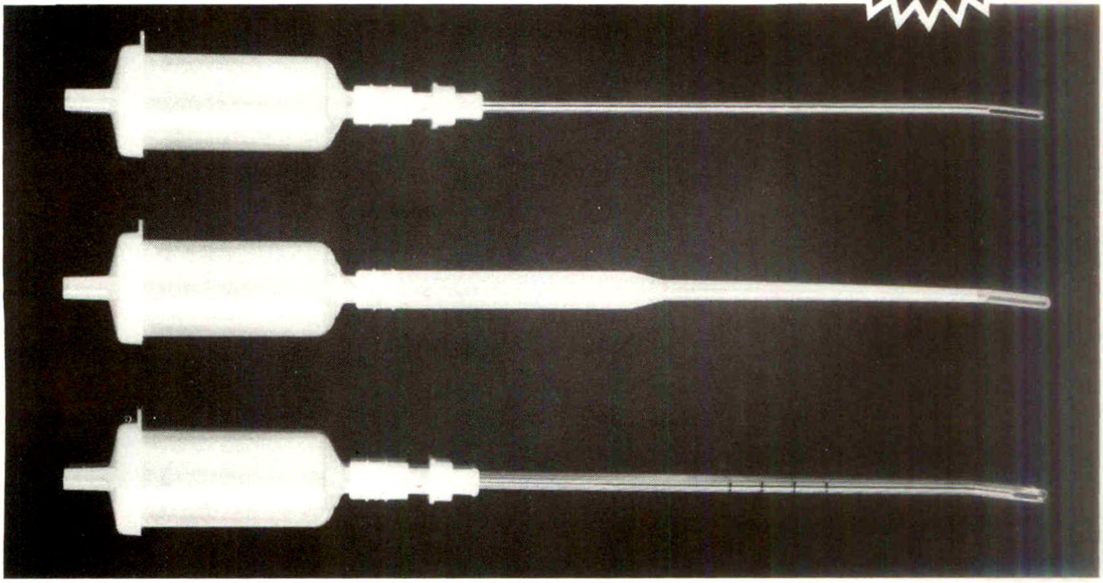

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COMMENTARY

Accuracy of the medical interview

The clinical interview is the most common procedure in medicine (Behrman & Vaughan 1983). This technique, which relies upon the memory of the informant, is used so often simply because it is the easiest way, and often the only way, to obtain many types of information about a patient (Haggard *et al.* 1960). Even though computerized data are now more widely accessible (Sheehan & MacAirt 1981) it has been suggested (Joffe & Grisso 1985) that computerized hospital records may be biased and are not necessarily more accurate than information obtained retrospectively by interview. In a survey of medical notes, Cartwright & Smith (1979) discovered inaccuracies and inadequacies and concluded that it would be inappropriate to assume that data such as artificial rupture of membranes, episiotomies or the admission of babies to intensive care units are accurately recorded. Nor were errors all in the same direction, since procedures were sometimes recorded in anticipation of being performed, and these intentions were not always carried out.

An additional major limitation of the medical record is the large amount of missing information (Tilley *et al.* 1985). When obstetricians were contacted by Tilley *et al.* (1985) in an attempt to obtain prenatal records for mothers of DES-exposed daughters, they were able to supply drug exposure data but frequently not the additional obstetric history requested. This reluctance to supply all the requested information was attributed by the authors either to the cost and inconvenience of copying records or to the physicians' fears of legal action. Mothers' questionnaires, in contrast, yielded much more complete information.

General practice records were also found incomplete when compared by Coulter *et al.* (1985) with the surgical histories of 198 patients in a postal survey. The authors comment that the incompleteness of the general practice records suggests that where it is important to obtain a full surgical history, patients' accounts are more reliable than their medical records.

The extensive use of history-taking interviews by doctors and researchers is reflected in only a small number of studies investigating the accuracy of information thus obtained. Respondent error may be assessed in terms of both the reliability and the validity of responses. The published research has focused less on the validity than on the reliability of respondent reports, that is, their stability over repeated measurements (Ridley *et al.* 1979). The relative lack of research on the validity of respondent reports on 'factual' items may reflect the difficulty in obtaining data with which to compare respondent reports. In addition, however, it is clear that in many cases the respondent is the best available source of valid information (Ridley *et al.* 1979).

Haggard *et al.* (1960) examined maternal interviews on attitudes, wishes, anxieties and 'hard facts' related to pregnancy and childbirth. They concluded that although some mothers gave reports that agreed reasonably well with what they had said previously, none of the mothers showed the degree of accuracy or reliability 'that one would hope for'. The 'hard facts' data, such as the length of child at birth were recalled best of all. Birth order and sex differences were found to have some influence on the recall of prior events in the clinical interview. In contradiction to the common assumption that more distant events will usually be recalled less well than more recent events, Haggard *et al.* (1960) found that the time interval, of itself, was not related to the reliability of the reported history.

Cartwright & Smith (1979) compared data from medical records and from interviews with women who had recently had a live birth or stillbirth. Maternal recall agreed reasonably well with hospital records regarding presentation of the newborn, use of instruments at delivery, caesarean section and epidural anaesthesia, whereas other types of anaesthesia, the reasons for drugs during labour and resuscitation of the baby, were less accurately remembered. Concordance between the two sources was generally less good for stillbirths than for live births.

Robbins (1963) studied the accuracy of parental recall of aspects of child-rearing practices. The parents were inaccurate in their memory of details about child-rearing practices and early developmental progress. Inaccuracies were greatest for items dealing with the age at weaning and toilet training, the occurrence of thumb-sucking, and demand feeding. In general, mothers' recall was better than fathers'.

The validity of mothers' reporting of the breast-feeding history of their children, more than 20 years after their birth, was studied in a Jerusalem population (Kark *et al.* 1984). Among 74 study subjects, duration of breast-feeding ascertained from an interview was well correlated with that recorded in mother-child health clinic charts. Concordance was similar in subgroups of ethnicity, mother's education, family size and sex of child.

In a series of studies undertaken to determine the extent to which reports can substitute for measurement in epidemiological investigations (Sorensen *et al.* 1983), the accuracy of self-reported weights and energy intake, and the accuracy of children's recall of their parents' weight 15 years earlier were found to be more accurate than had been generally believed. Furthermore, the error in reporting can be predicted, permitting such reports to be used with a high degree of confidence.

The association between dietary patterns and cancer incidence led Jensen *et al.* (1984) to investigate how accurately persons can recall their dietary habits after 15–25 years. The authors found a positive, although barely significant, correlation between diet information from a household survey conducted either 15 or 25 years earlier and interview information on current and past diet. The recall of past diet was strongly influenced by present dietary habits. The validity of patients' family medical histories was examined by Harris *et al.* (1980). Although most patients knew the age and cause of death of their parents, fewer than half knew this information for grandparents. Cancer patients had significantly better recall of maternally related relatives. A comparison of patients' family medical histories with death certificate data found patient reports to be inaccurate.

The surgical histories provided by 198 subjects in response to a postal survey were compared with the records of surgical operations contained in their general practice notes (Coulter *et al.* 1985). Agreement between the two data sources was 90% for type of operation and 82% for the year of operation. Although 18% of the dates of operations were inaccurate, about 66% of them were within 3 years of the correct date. There was no evidence of overreporting of operations and no evidence that subjects had failed to report any major operations. It was concluded that surgical operations are relatively well-remembered events.

Marital and fertility histories were collected from elderly women by Ridley *et al.* (1979). Events of high social importance such as births and marriages showed the highest levels of reliability and ease of recall. For less salient events, retrospective reporting was likely to suffer from response error. The study found little evidence of differentials in recall ability and reliability by respondents' age, education or current health status.

The recall of menstrual histories of a sample of 160 women who had previously recorded their menstrual and reproductive events as they occurred, was reported by Bean *et al.* (1979). For age at menarche, age at natural menopause, age at surgical menopause and age at first use of oral contraceptives, the percentage of women who correctly recalled within a year ranged from 75% to 90%. Recollection of menstrual cycle length and variability was unreliable. These results on the accuracy of recall of age at menarche are comparable with data from other studies.

The accuracy of patient recall of spontaneous and induced abortions has been investigated. Wilcox & Horney (1984) reported that 75% of recorded abortions were recalled by 348 women who had participated in the Menstrual and Reproductive Health Study and were resurveyed regarding their pregnancy histories. Gestational age at the time of abortion was the major determinant of recall, with early abortions less often remembered. Time since abortion also affected recall but less so. Parity and maternal age were not related to completeness of recall. Wilcox & Horney (1984) concluded that the recall of 75% of recorded spontaneous abortions among women sensitized to their reproductive functions probably represents an upper limit of recall for other populations.

Of a group of women who underwent induced abortions and subsequently gave birth, 16% denied the abortions in a medical interview following their next delivery (Slater & Davies 1978). Religious women and women with fewer children had a greater tendency to deny than others. The authors could not determine whether the failures to report the induced abortions were deliberate or whether they resulted from selective recall.

In a recent study Tilley *et al.* (1985) compared maternal pregnancy history recall and medical records. In general, there was 'good to excellent' agreement for recall of personal history (past abortions and pregnancies). However, for pregnancy problems (threatened abortion, hospitalization during pregnancy other than at delivery) agreement was 'poor to good', and for medical intervention such as drugs and X-rays, agreement was poor.

Despite the popularity of computerized data banks, access to the hospital records of individual patients remains limited, and physicians will thus continue to rely extensively on the clinical interview. Studies examining the accuracy of patient recall reveal considerable variation in both reliability and validity. This variability is related both to patient characteristics and to the type of information sought. Recall accuracy is not necessarily affected by length of time elapsed since the event or respondent age or education. Details of seminal life events, such as first births, and numerical data, such as birthweight and gestational age, are well-recalled, and can generally be considered accurate.

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British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 724–730

Adverse long-term effects of oral contraceptives: a review

R. W. SHAW

In the early 1960s when combined oral contraceptives were first made available for widespread use they were thought to be close to the ideal method of contraception, meeting criteria of safety, efficacy, reversibility, acceptability, non-temporal relation to coitus and cost. In the late 1960s some of the earlier retrospective epidemiological investigations on the adverse effects of oral contraception were published (Inman & Vessey 1968; Sartwell *et al.* 1969). In recent years more complete prospective studies on large populations have assessed the morbidity and mortality associated with the use of oral contraceptives. Each new set of published data may alter our perception of the risk/benefit ratio but in some way adds to the confusion.

Two studies on the use of oral contraceptives and the incidence of breast cancer (Pike *et al.* 1983) and cervical neoplasia (Vessey *et al.* 1983*a*) further stimulated concern and debate. Since then there have been other studies and the aim of this review was to bring together the available data on the adverse effects of oral contraceptives with regard to malignant tumours and cardiovascular disease.

It is difficult to assess the safety of oral contraceptives because formulations and dosages have changed markedly since they were first introduced. Many patients stop and start using preparations, change to other formulations so that it becomes difficult for epidemiological studies to assess the inter-relation between current and ex-usage of oral contraceptives and particularly the effect of specific formulations.

Malignant tumours

Breast cancer

Breast cancer is a major cause of cancer mortality amongst women. It is estimated that 1 in 17 women in the UK ultimately develop the disease. Many of the risk factors for breast cancer, such as early age at menarche, late age at first birth and late age at menopause are related to a woman's hormonal status (Kelsey 1979). It is not surprising that concern about the possible adverse effects of oral contraceptives appeared as early as 1969 (Hertz 1969).

Breast tissue is responsive to ovarian hormones and during the menstrual cycle there are changes in breast volume, histology and also in DNA synthesis which may be relevant to possible carcinogenesis. DNA synthesis decreases during the first half of the normal menstrual cycle but after ovulation, when progesterone is synthesized, there is a marked rise in epithelial activity which depends on the prior exposure to oestrogen (Masters *et al.* 1977). Data on the effects of oral contraceptives on breast epithelial activity was reviewed by Anderson (1984), and morphological studies in the resting breast showed no difference in parenchymal mitotic response between users and non-users of oral contraceptives.

Kalache *et al.* (1983) reviewed both case-control and cohort studies on oral contraceptives and breast cancer. The available epidemiological evidence was reassuring but amplified some of the shortcomings in several of the previous published studies. The reports of two large case-control studies (Rosenberg *et al.* 1984; Vessey *et al.* 1983*b*) are in general very reassuring as indeed is the study from the Centers for Disease Control (1983*a*) on long-term effects in which no association could be found between breast carcinoma and duration of usage of oral contraceptives.

It has been suggested previously that the use of oral contraceptives before the first full-term pregnancy might increase the risk of breast cancer (Paffenbarger *et al.* 1980; Pike *et al.* 1981). This was not confirmed in the Centers for Disease Control study (1983*a*) when taking into account confounding factors such as age at first

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pregnancy and menopausal status which reduced the relative risk to 1·3. Thus, the use of oral contraceptives does not appear to increase the risk of breast cancer appreciably more than any other form of delaying the first full-term pregnancy.

Rosenberg *et al.* (1984) also found no association between long-term oral contraceptive use and increase of breast cancer, even after >10 years of oral contraceptive usage before the first pregnancy, except for women whose first pregnancy occurred at ⩾35 years of age. However, these findings were based on very small numbers. In contrast Ollson *et al.* (1985) found that the relative risk for breast cancer increased with the earlier age at the start of pill usage and a possible correlation with the age at first full-term pregnancy. Although that study was relatively small, the findings supported the suggestion from Pike *et al.* (1983) that the long-term use of oral contraceptives before the age of 25 increased the risk for breast cancer.

The published cohort studies summarized by Kalache *et al.* (1983) again are reassuring, bearing in mind that the number of women who have developed breast cancer so far is still fairly small, particularly in some of the sub-groups which may have increased risk factors.

Two other recent case-control studies failed to provide evidence that the use of oral contraceptives increased the risk for breast cancer. In one of these studies (Centers for Disease Control 1986) even ⩾15 years of oral contraceptive use did not increase the incidence of breast cancer and there was no association between any specific oral contraceptive formulation and the risk for breast cancer. The second, a national study from New Zealand, showed a relative risk of 0·94 for breast cancer in women who had ever used oral contraceptives and this increased to 2·2 in women aged 25–34 at diagnosis. An analysis of risk by duration of use, age at first use and time since first use showed no adverse effect of oral contraception (Paul *et al.* 1986).

These studies provide further evidence against the hypothesis that use of oral contraceptives at young ages increases the risk of breast cancer but whereas most use of oral contraceptives occurs early in a woman's reproductive life, the risk of breast cancer occurs later. We may still have to wait 10 years or more before we can be confident to assess adequately the possible carcinogenic effects of the pill in the long term. The data to date also fail to indicate any specific formulation which may be more detrimental than any other.

Cervical cancer

The influence of sexual behaviour with regard to age of first intercourse, the number of partners, infection—particularly with herpes and papillomavirus—and cigarette smoking have been thought to be risk factors in the aetiology of cervical neoplasia. Investigations about links between the use of oral contraceptives and cervical neoplasia present special problems with regard to identifying groups of women for comparison who have the same intrinsic risk of disease, allowing for confounding variables of sexual practice of the patients (and their partners), ensuring equal surveillance with cytological testing and recognizing that alternative methods of contraception, particularly occlusive methods, offer some protection against the disease.

A number of epidemiological studies have been published on oral contraception and the risk of cervical neoplasia. Case-control studies by Worth & Boyes (1972), Thomas (1972) and Boyce *et al.* (1977) could find no relation, but they included very few long-term oral contraceptive users. Other studies by Ory *et al.* (1977) and Harris *et al.* (1980) found a positive association between risk and duration of use. Cohort studies have likewise tended to produce positive results as in the Walnut Creek Study (Peritz *et al.* 1977), but Swan & Brown (1981) suggested subsequently that these results could have been due, to confounding differences in sexual activity between users and non-users and with durations of use. Data from the Oxford Family Planning Association contraceptive study (Vessey *et al.* 1983*a*) compared the incidence of cervical neoplasia in parous women between those using oral contraception and those using an intrauterine contraceptive device (IUCD). Cervical neoplasia (invasive carcinoma, carcinoma-in-situ and dysplasia) occurred more frequently in the oral contraceptive group. The incidence of all forms of neoplasia rose from 0·9/1000 woman years in women who had used oral contraceptives for 2 years, up to 2·2/1000 woman years in those with more than 8 years' use, compared with a constant rate of about 1/1000 woman years in IUCD users. Preliminary results from a multi-centre hospital-based case-control study (WHO Collaborative Study 1985), largely from developing countries, reported a relative risk of 1·19 for invasive cervical carcinoma in women who had ever used oral contraception, and the relative risk increased with duration of use to 1·53 after 5 years' use. The relevance of this study has been questioned on several grounds including the types of preparations used which are substantially different from those currently used in this country. The authors stressed that the results should be interpreted with caution since the overall relative risk of 1·19 in women who had ever used oral contraception was of borderline significance and could be due to incomplete control groups and confounding effects of sexual variables; moreover no data on smoking habits were available.

Data from UK national statistics published by the Population Census and Surveys show a progressive increase in the incidence of cervical cancer in women born after about 1935, and that this change took place in 1960 approximately (Doll 1985); this would suggest that other factors were affecting the incidence before the use of oral contraceptives became widespread.

In summary, the published data do suggest that the use of oral contraception is associated with a higher incidence of cervical intraepithelial neoplasia (CIN) with a possible link with duration of use. However, it would seem that oral contraceptives may promote, rather than initiate, neoplasia in patients at risk. Most patients in these studies had pre-invasive disease and it should therefore be possible to identify them with regular cytological screening and treat these lesions before they progress. Further work is required to elucidate the aetiological role of oral contraception and close supervision of patients is most important.

Cancer of the ovary and endometrium

Newhouse *et al.* (1977) were the first to suggest that oral contraception might protect against ovarian cancer. Other case-control studies (Rosenberg *et al.* 1982; Centers for Disease Control 1983*b,c*) have indicated that oral contraception reduces the risk of both ovarian and endometrial carcinoma to about half that in non-users. These protective effects increase with duration of use and persist perhaps for some years after discontinuation of pill use.

Major cohort studies still include too few of these cancers for firm conclusions to be drawn. Both these tumours can be difficult to detect in their early stages and their combined incidence is about equal to that of cervical neoplasms. It has been argued that this protective effect of oral contraception might counterbalance the possible increased incidence of cervical neoplasia. However, it seems likely that patients at risk for ovarian and endometrial carcinoma are not those most likely to develop cervical carcinoma.

Other tumours

It has been suggested that oral contraceptives increase the risk of prolactinoma of the pituitary gland but findings in two case-control studies (Shy *et al.* 1983; Pituitary Adenoma Study Group 1983) provide strong evidence against this association. Early prolactinomas have been diagnosable only in recent years, and clinicians should be aware of the possible presence of a prolactinoma in patients with menstrual irregularity and consider this before prescribing oral contraception.

Hepatocellular adenomas, although extremely rare (perhaps 1–2 per 100 000 users per annum), do appear to occur more frequently in women using oral contraceptives than in non-users (Edmondson *et al.* 1976; Rooks *et al.* 1979). The risk seems to be greater in older women who used high-dose preparations over a long period of time (Rooks *et al.* 1979).

The development of hepatocellular carcinoma has also been reported but only very rarely (Henderson *et al.* 1983). The evidence that oral contraceptives may cause primary hepatocellular carcinoma has come from uncontrolled studies (Neuberger *et al.* 1986), but for young women the number of cases reported in the UK has increased slightly since the mid 1960s when the use of oral contraceptives became widespread. A recent case-control study (Forman *et al.* 1986) showed that oral contraception was associated with a higher relative risk of 3·8 for hepatocellular carcinoma and ≥8 years' use was associated with an increased relative risk of 20·1. There was no increased risk for cholangiocarcinoma. These authors commented, however, that the small number of cases available for analysis made the estimation of the relative risk imprecise. In the UK, hepatocellular carcinoma remains an exceptionally rare disease especially in young women. However, in those countries where it is more common, the contributory role of oral contraceptives needs further close study.

Cardiovascular effects

Anecdotal case reports of stroke and pulmonary embolism in women using oral contraception began the investigations on adverse cardiovascular problems associated with oral contraceptives. Case-control retrospective studies on various cardiovascular problems began to appear in the late 1960s and continue but were often restricted to a known range of diagnoses and thus tended to support certain anecdotal reports. There have been three major prospective studies on the effect of oral contraception, two in the UK by the Royal College of General Practitioners and the Oxford Family Planning Study, and one in the US, the Walnut Creek oral contraceptive drug study. Interpretation of results of these studies is made difficult because patients were selected on a non-random basis at enrolment and at the time the studies began, clinicians were beginning to recognize the possible adverse cardiovascular effects of oral contraceptives and may have allocated patients with risk factors to the control group. This would tend, if anything, to reduce the incidence of problems in the group using oral contraceptives.

However, an increased risk for all categories of cardiovascular disease in association with oral contraception has never been demonstrated, and the risk does not apply to all users and there may well be important differences associated with the use of different combined preparations.

Realini & Goldzieher (1985) produced an extensive critique of published epidemiological studies on oral contraception and cardiovascular disease which assessed all the possible biases in the case-control, cohort and mortality statistics studies.

Arteriosclerosis and coronary heart disease

Substantial evidence now links alterations in blood lipid and lipoprotein levels to arteriosclerosis and coronary heart disease. The use of oral contraceptives produces changes in serum lipid and lipoprotein levels but the significance of these changes is not certain. The fact that oral contraceptives affect lipid metabolism has been known for some time since Wynn *et al.* (1966) demonstrated these changes. In general high density lipoprotein (HDL) levels are found to fall with increasing dose and potency of progestogens and to rise with increasing doses of oestrogen (Bradley *et al.* 1978), whilst very low density lipoprotein (VLDL) show variable responses. Although lipoprotein fractions may alter in women using oral contraceptives, they generally remain within the normal range in most users, so that it is difficult to assess the long-term implications for any one woman.

It is now believed that both the oestrogen and progestogen components of the pill contribute to the incidence of arterial disease (Mann *et al.* 1975; Kay 1982). Further studies demonstrate that the heart attacks occur mainly in women with additional risk factors—increasing age and smoking. Women who smoke are 2–4 times as likely to have heart attacks as non-smokers (Kunin *et al.* 1969). Other risk factors include hypertension, high level of VLDL and diabetes (Kay 1982; Mann *et al.* 1975).

It would seem prudent then to restrict oral contraception to patients without added risk factors and to prescribe preparations that have the least impact on the woman's metabolic indices. Indeed this has been the philosophy behind the marketing of recent preparations and of current prescribing. We must wait to see if this policy will influence the incidence of disease in the future.

Hypertension

Hypertension is accepted as one of the proven side-effects of oral contraception and can occur in an acute or chronic form. A number of studies report a mild elevation in systolic blood pressure but no change in diastolic (Clezy *et al.* 1972; Kunin *et al.* 1969).

The risk of developing hypertension with oral contraception increases with age and duration of usage (Royal College of General Practitioners 1974). What effects hypertension, even though mild, may have over a prolonged period on the cardiovascular system are not known. However, there appears to be no increased incidence of hypertension in women who have used oral contraception previously when compared with a matched control group of non-users (Royal College of General Practitioners 1974).

Venous thromboembolism

Case-control and cohort studies found a positive association between oral contraception and occurrence of idiopathic venous thromboembolism, whereas most of the mortality statistics studies reported either equivocal or negative results (Realini & Goldzieher 1985).

All studies on venous thrombosis are plagued with problems of confirmatory diagnosis of the disorder. In general there seems to be overall agreement that the incidence is reduced with lower doses of oestrogen in the contraceptive preparation. Porter *et al.* (1985) put the risk of venous thromboembolic disease in current pill users at 0·08/1000 woman years compared with 0·04/1000 woman years for non-users, a rate ratio on their data of 2·8 for pill users compared with non-users. Past history of venous thromboembolism must still remain an absolute contraindication for oral contraception.

Cerebrovascular accidents

The question of an increased risk of subarachnoid haemorrhage remains controversial. Reports from Petitti & Wingerd (1978) and the Collaborative Group for the Study of Stroke in Young Women (1973) support the suggestion, whilst two careful case-control studies (Inman 1979; Thorogood *et al.* 1981) showed only a small increase which was not statistically significant and there was no excess risk apparent in the Oxford Family Planning Association prospective study (Vessey *et al.* 1981).

The suggestion that the use of oral contraceptives might increase the risk of stroke was made over 20 years ago and controlled studies of this problem are few. The Oxford Family Planning Association Study (Vessey *et al.* 1984) suggested that the risk of non-haemorrhagic stroke is greater in women using oral contraceptives but the increased risk is confined to current users and is small at a rate of 0·30/1000 woman years for current users of >36 months duration. This supports the findings of the Collaborative Group Study on Strokes in Young Women (1973) that the incidence of non-haemorrhagic stroke is not adversely affected by hypertension or smoking but current users of oral contraceptives had an increased risk although duration of use was not a contributory factor.

The two most important factors which influence the risk of dying from all forms of cardiovascular disease in users of oral contraceptives are cigarette smoking and age (Royal College of General Practitioners' Oral Contraception Study 1981). The relative risk for women who smoke is consistently higher, age group by age group, than for non-smokers. It is substantially higher in the age groups 35–44 and ≥45 years in smokers. No such increase in deaths was observed in the Walnut Creek study which questioned the proposition that oral contraceptives cause cardiovascular diseases (for review see Wiseman 1984). However, there seems to be a possible risk of certain cardiovascular events associated with oral contraception and this needs to be taken into account when weighing the risks and benefits in choosing the best preparation for each patient.

Conclusions

A great deal is now known about the adverse long-term effects of oral contraception although the data from case-control retrospective studies often conflict with those from prospective studies. Because oral contraceptive preparations have changed in recent years and because some tumours (breast in particular) develop more often in later life when oral contraception is no longer used, it may be another decade before the true picture can be assessed.

However, available data have suggested increased risk factors for certain types of cardiovascular disease related to age, smoking, hypertension and use of oral contraceptives. These criteria have been utilized for some years by clinicians when selecting patients suitable for oral contraception and have probably already made an impact.

The more recent reports of an increased incidence of CIN in women using oral contraceptives require close scrutiny and assessment with cervical screening programmes to elucidate whether oral contraceptives are acting as initiating or merely promoting agents, as seems more likely at present. The data on breast cancer and oral contraception seem encouraging at present with no increased incidence. However, they must be tempered by the fact that another 10 years may need to pass before current 'at risk' patients may develop the disease.

Oral contraception is widely used by young, healthy women who expect their physicians to prescribe safe drugs which will not harm their health. The profession is monitoring carefully all aspects of pill use, and it is hoped that the newer formulations, with their lower overall doses of oestrogen and progestogen, will provide preparations which cause an even smaller incidence of problems both currently and in the long term.

Acknowledgments

This report was prepared by Professor R. W. Shaw at the instigation of the Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists. Helpful comments have been received from members of that committee but the final views and conclusions are those of Professor R. W. Shaw. I would also like to thank Organon Laboratories Limited, Ortho-Cilag Pharmaceutical Limited, Parke Davis Research Laboratories, Schering Chemicals Limited, Searle Pharmaceuticals and Wyeth Laboratories, for providing some background review data.

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Received 1 September 1986
Accepted 22 December 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 731–735

Accuracy of mothers' recall of birthweight and gestational age

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Summary. Information on the birthweight and gestational age of previous siblings is usually dependent upon maternal recall. This information is of importance in assessing the current risk of perinatal morbidity and mortality. The validity of maternal recall of birthweight and gestational age of 880 children born to 97 multiparas was examined by comparison with hospital records. About 75% of all reported birthweights were accurate to within 100 g and a similar proportion of reported gestational ages was correct to within 1 week. Recall was most accurate for most recent births as well as for earliest births and was not related to maternal age or education. There was a tendency for the smallness of low birthweight infants to be exaggerated by mothers. We conclude that within defined limitations, maternal recall of birthweight and gestational age of previous children is sufficiently accurate for clinical and even for epidemiological use.

Data on birthweight (BW) and gestational age (GA) of previous births are frequently obtained at obstetric and paediatric maternal interviews. The accuracy of this information is important as BW of the previous sibling has been found to be a highly significant predictor of BW, even after controlling for the GA of the propositus (Anderson *et al.* 1984). Similarity in BW among siblings prevails even after adjusting for length of gestation, sex, birth order and maternal height (Tanner *et al.* 1972). The risk of a light- or heavy-for-gestational age infant, when the previous sibling had been of low or high birthweight for gestational age, respectively, is increased (Ounsted *et al.* 1985). The tendency to similar GA and BW in successive births should be taken into account in the recognition of intrauterine growth retardation (Turner 1971) and has significant implications in terms of perinatal mortality (Bakketeig *et al.* 1979; Bakketeig & Hoffman 1983). If a newborn infant differs considerably from its expected size or age, the risk of perinatal mortality is increased even in relation to other infants of similar size and weight. This implies that perinatal mortality risk should be assessed not only in relation to GA and BW but also with respect to the fetal age and body measurements of older siblings (Bakketeig & Hoffman 1983).

Tanner *et al.* (1972) have suggested that a within-family BW standard would allow better differentiation between babies with 'impaired uterine growth' and 'physiological smallness'. Thus comparison with the GA and BW of older siblings will exclude from 'risk' a considerable number of newborns who would be classified by the use of population standards as light-for-gestational age (LGA). One may assume that these are simply physiologically small babies born to mothers who habitually produce small babies.

Previous studies (Table 1) which have

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Table 1. Maternal recall of birthweight

Study	Interval since birth (years)	No. of subjects	Accurate ± 50 g	Accurate within 225 g
Pyles *et al.* (1935)	2	223	59%	Correlation coefficient: 0·96
Cartwright & Smith (1979)	0·25–0·33	131	—	82%
Robbins (1963)	3	43	58%	86%
Axelsson & Rylander (1984)	0–7	551	88%	93%*
Haggard *et al.* (1960)	7–8	19	—	Reliability coefficient: 0·71
Present study	0–23	662	41%	87%†

* Within 100 g.
† Within 200 g.

assessed the validity of maternal recall of BW and GA systematically have varied from one another in many respects, including size of the study population, length of interval since birth, and statistical methods. Because the degree of accuracy of maternal recall of GA and BW is still felt to be an unsettled issue, we undertook a study to examine the accuracy of maternal recall of gestational age and birthweight over a wide range of intervals since birth and parity. A large group of grand multiparae from the economically and ethnically homogeneous population of Mea Shearim, Jerusalem, were interviewed and BW and GA recall compared with data recorded in hospital records. By obtaining information from this special sample of grand multiparae, we had a unique opportunity to assess, in a longitudinal way, the ability of the same women to recall BW and GA after various time intervals between birth and interview. The influence on maternal recall of birth order, low BW and the mothers' age, education and ethnic origin, was also studied.

Subjects and methods

The study included 97 women, giving birth to at least their 7th child between April 1984 and January 1985, at Bikur Holim Hospital, who were interviewed about the outcome of all their previous pregnancies. The mothers had given birth to 880 children during the previous 23 years, 90% of them at two Jerusalem hospitals, Bikur Holim (65%) and Shaare Zedek (25%). The BW and GA reported by each mother were compared with the birth records at these two hospitals. For the purposes of our study, the birthweight and gestational age recorded at the time of the birth in question were assumed to be correct.

Bikur Holim Hospital serves a unique population. The vast majority of the grand multiparae are ultra-orthodox Jews from the nearby Mea Shearim community. As birth control is forbidden by Jewish religious laws, fertility is extremely high, and the grand multiparae are relatively young. This community has a family-size-linked socio-economic system that ensures a minimum income per family member.

In the present study, the grand multiparae were all Jewish, 82% of them of Ashkenazi origin. Approximately 80% of the mothers had attended high school and 25% had additional university or technical education. The mean maternal age at interview was 35 (SD 8) years.

Agreement of BW and GA between hospital records and maternal interviews was calculated and tabulated by time interval since birth and by birth order. The accuracy of BW recall was also analysed by maternal age, education and ethnic origin, and by the child's recorded BW.

Analysis of variance of mean errors in BW recall in subgroups of birth interval, birth order, maternal age, education and ethnic origin was made with the help of the SPSS ANOVA subprogram (Nie *et al.* 1975).

Results

Data were available from hospital records to check maternal recall of BW in 84% of cases and GA in 68%.

Maternal recall of BW was found to be highly accurate (within 10 g) in 41% of the cases, accurate to within 100 g in 75% and to within 200 g in 87%. It was more than 300 g off target in 8%.

Recall of BW (Table 2) was best for birth order 1 and 10–12, worst for birth orders 4–6, and about the same for birth orders 2–3 and 7–9. Analysis by interval since birth (Table 2) showed that BW recall was best for the shortest interval

Table 2. Maternal recall of birthweight by birth order and interval since birth

Birth order	Mean birthweight error (g) by interval since birth (years)					
	0–4	5–9	10–14	15–19	20–23	Total (mean ± SD)
1	—	90	68	38	147	61 ± 142
		(3)	(27)	(23)	(3)	(56)
2–3	—	78	88	62	300	88 ± 160
		(25)	(78)	(24)	(4)	(131)
4–6	86	147	128	87	—	129 ± 242
	(35)	(109)	(81)	(11)		(236)
7–9	52	122	94	45	—	77 ± 124
	(105)	(59)	(14)	(2)		(180)
10–12	42	135	0	—	—	57 ± 148
	(45)	(11)	(3)			(59)
Total						
mean	56	130	100	57	234	95
±SD	±113	±254	±153	±83	±437	±185
n	(185)	(207)	(203)	(60)	(7)	(662)

The number of subjects is shown in parentheses.

(0–4 years) and worst for birth intervals 5–9 years and 20–23 years. Recall was remarkably accurate for births 15–19 years preceding the interview. The variations in recall error among the different subgroups of birth interval and birth order were statistically significant ($P<0{\cdot}01$). Birthweights of low birth order infants were exceptionally well recalled at all intervals since birth (Table 2). Accuracy of recall was not statistically significantly related to maternal age or education (Table 3). In our population, mean maternal age at first birth was 21·0 years. This variable was not related to accuracy of BW recall.

The three women born in Asian and the four born in North African countries, although few in number, recalled the birthweights of their previous children significantly less accurately ($P<0{\cdot}01$) than the 66 women born in Israel or the 20 born in other countries. There was no statistically significant difference in the accuracy of BW recall between the 77 women of Ashkenazi origin and the 16 women of Sephardic Jewish origin.

Mothers of low birthweight babies (≤2500 g) tended to exaggerate their smallness. Mothers of both high (<4000 g) and low BW babies tended to be more accurate in their recall of BW (Table 4).

Maternal recall of GA was found to be completely accurate in 39% of the cases, accurate to within 1 week in 74%, and to within 2 weeks in 94% of the cases. No difference in recall of GA was found in the various parity groups or by interval since birth.

Discussion

More than 50 years ago, Pyles *et al.* (1935) showed that maternal recall of the birthweights of their children correlated well with recorded birthweights.

Haggard *et al.* (1960) assessed the validity of the interview in 19 mothers of 7–8-year-old chil-

Table 3. Maternal recall of birthweight by maternal age and education

	Birthweight error (g) mean (SD)	*n*
Maternal age (years)		
27–34	123 (78)	27
35–36	80 (51)	21
37–38	82 (72)	22
39–48	119 (148)	23
Unknown	— —	4
Total	102 (92)	97
Years of maternal education		
0–8	99 (68)	19
9–12	90 (84)	50
≥13	132 (118)	24
Unknown	— —	4
Total	102 (92)	97

Table 4. Accuracy of maternal recall of birthweight

Infant birth-weight (g)	Birthweight error* (g) mean (SD)	*n*
≤2500	56 (75)	20
2501–3000	83 (144)	129
3001–3500	87 (132)	279
3501–4000	120 (262)	198
>4000	72 (193)	39
Total	94 (185)	665

* Compared with hospital records

dren. They found that the mothers' statements during the interview were often not accurate, but that 'hard fact' data such as BW was recalled best of all. (The coefficient of interclass correlation was R=0·71).

Robbins (1963) examined the accuracy of parental recall of aspects of child development by 43 mothers of 3-year-olds. When questioned about their child's BW, 58% reported accurately, 28% deviated by <½ lb and 14% by ≥½ lb. Fathers' recall was far less accurate.

Information from a questionnaire on pregnancy outcome completed by 782 women engaged in laboratory work was compared with data in hospital records and central registries (Axelsson & Rylander 1984). In 28% of infants, reported birthweight disagreed with that recorded 7 years earlier in the Swedish Medical Birth Register, but the difference exceeded 100 g in only 7% of cases.

Tilley *et al.* (1985) using data from the Diethylstilbestrol-Adenosis project, compared prenatal records with obstetric history from mothers' questionnaires completed ≥10 years after the birth of their daughters. BW was divided into three groups, high (≥ 4000 g), low (<2500 g) and average (2500–3999 g); 95% of the 2539 mothers correctly identified the BW group of their babies.

Comparing data from medical records with information from interviews with 131 women who had a live birth and 109 who had a stillbirth, Cartwright & Smith (1979) found that among the live births, reports of birthweight fell within ½ lb of true birthweight in 82% and within 1 lb in 94%. The level of agreement was slightly lower for the stillbirths: 80% and 87%, respectively. When mother and doctor were asked about the length of gestation in weeks, the correlation between the data from the two sources was 0·78 for the live births and 0·80 for the stillbirths.

Sheehan & MacAirt (1981) checked the reliability of mothers' recall of birth data; 99 mothers of children 4 and 6 years of age were studied. The authors concluded that within limits of random variation, mothers' recall of GA (44% completely accurate) could be taken as valid. Though no numerical data were given, they stated that BW recall was not generally accurate. Recall validity was associated with social class of mother, age of child at examination, and low BW. The recall of mothers of average weight children was said to be valid. The tendency of mothers of low BW infants to exaggerate their smallness (Sheehan & MacAirt 1981), was also found in the present study, but to a lesser extent.

Joffe & Grisso (1985) compared postpartum hospital records with interview data. They found that internal inconsistencies within hospital case notes were highly associated with BW, being more extreme for babies with low BW. This led them to suggest the possibility of bias when hospital records are used for the investigation of conditions associated with low BW, and to dispute the assumption that concurrent recording in hospitals is always superior to the information obtained retrospectively by interview.

Social class of the mothers in our study was generally homogeneous, and therefore we were unable to assess its influence on maternal recall. The number of years of maternal education did not affect accuracy of recall. This was in contradiction to studies conducted decades ago (Pyles *et al.* 1935; Robbins 1963), in which higher educational status was correlated with more accurate recall. The positive association between maternal education and accuracy of recall is not a universal finding, however (Ridley *et al.* 1979).

Haggard *et al.* (1960) have suggested that birth order might influence recall in an interview, although Sheehan & MacAirt (1981) found no evidence that parity affects mother's recall of BW. Our unique data set made it possible to examine BW recall in a wide range of birth orders. The high birth-order group was recalled best, as expected. The unexpected observation that low birth orders were recalled very accurately could be explained by the relatively high anxiety related to early deliveries. It has been shown (Haggard *et al.* 1960) that if anxiety is associated with specific experiences it seems to facilitate the accurate recall of those experiences. In our study, maternal recall of the BW of first births, an average of 14 years later, was remarkably accurate (89% within 100 g). First births were those best recalled in every time interval since birth.

The time interval from birth to interview was not related to validity of recall in Haggard's study (1960). On the other hand Sheehan & MacAirt (1981) found that as the age of the child increased, the size of the recall error became larger.

The wide span of intervals since birth in the present study was much greater than in any previous examination of maternal recall. Furthermore, it is the only study known to us that examines the recall of the same mothers after several different time intervals, thus presenting a longitudinal assessment of maternal memory. No direct relation was found between the length of time since birth and the accuracy of recall. BW of early deliveries was most accurately remembered after intervals of more than 15 years, reflecting the special mark left by first and also second births in maternal memory.

Ley (1972) has shown in several investigations that medical information is best recalled by patients when it is (a) told first and (b) considered most important. After the infant's sex, BW is usually the first piece of information given to the mother following the birth of a normal child. This 'primacy effect', in addition to the importance commonly attached to BW as a reflection of the newborn's well-being, apparently has a positive effect on the accuracy of maternal recall.

We conclude that maternal recall of BW and GA can be taken as valid, although differences among mothers do exist. The validity of maternal recall of BW was not correlated with time interval since birth, or with maternal age or education. Recall was exceptionally high for the low birth orders, even after 15 years.

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Received 16 December 1985
Resubmitted 20 January 1987
Accepted 31 March 1987

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 736–741

The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relation to fetal behavioural states in normal pregnancy at 37–38 weeks

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Summary. The relation between the blood flow velocity waveform in the fetal internal carotid artery ($n = 12$) and umbilical artery ($n = 15$) and fetal behavioural states at 37–38 weeks of gestation was studied. In the fetal internal carotid artery, under standardized fetal heart rate conditions, the pulsatility index (PI), as a measure of peripheral vascular resistance, was significantly lower during behavioural state 2F (active sleep) compared with state 1F (quiet sleep) according to the classification by Nijhuis *et al.* (1982), suggesting increased fetal cerebral blood flow during state 2F. In the umbilical artery, no significant difference in PI between the two behavioural states could be established. This suggests a fetal origin of the state dependency observed in fetal blood flow velocity waveforms.

In normal late pregnancy fetal behavioural states have been shown to affect blood flow velocity waveforms in the lower thoracic part of the fetal descending aorta. Using the classification of Nijhuis *et al.* (1982), the pulsatility index (PI) was significantly lower during behavioural state 2F (active sleep) than during behavioural state 1F (quiet sleep) (van Eyck *et al.* 1985). It was suggested that these changes may reflect an increased perfusion of the fetal skeletal musculature during behavioural state 2F.

Recently, a Doppler ultrasound method for recording the blood flow velocity waveform in the fetal internal carotid artery was developed (Wladimiroff *et al.* 1986). The question arises, whether fetal behavioural states also affect fetal blood flow in the internal carotid and umbilical arteries. This may be of clinical importance since flow velocity waveforms in both vessels are now being increasingly studied to identify intrauterine growth retardation (Giles *et al.* 1982; Schulman *et al.* 1984; Reuwer *et al.* 1984; Trudinger *et al.* 1985; Wladimiroff *et al.* 1986, 1987).

If a fetal regulatory mechanism is responsible for the observed state-dependent changes in the fetal descending aorta, then state-dependent changes could also be expected in the fetal internal carotid artery with state independency in the umibilical artery.

The objective of the present study was to establish the relation between the blood flow velocity waveform in the fetal internal carotid and umbilical artery and fetal behavioural

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states, in particular states 1F and 2F during normal late pregnancy.

Subjects and methods

A total of 15 normal subjects with singleton pregnancies at 37–38 weeks gestation consented to participate in the study. The gestational age had been calculated from a reliable menstrual history and early ultrasound measurement of fetal crown-rump length or biparietal diameter. Fetal birthweight was between the 25th and 90th centile for gestational age according to Kloosterman's Tables corrected for maternal parity and fetal sex (Kloosterman 1970). All subjects were non-smokers and no medications were prescribed. All studies were performed 2 h after breakfast or lunch, with the subject in the semi-recumbent position. A combined mechanical sector scanner and pulsed Doppler system (Diasonics CV 400) was used in 12 subjects for recording the maximum flow velocity waveform in the fetal internal carotid artery at the level of the bifurcation into the middle and anterior cerebral artery (Wladimiroff *et al.* 1986) and in 15 subjects for recording the maximum flow velocity waveform in the umbilical artery. Only recordings depicting simultaneous arterial and venous flow velocity patterns were accepted as originating from the umbilical cord. Venous blood flow had to be constant to ensure fetal apnoea.

Maximum flow velocity waveforms were recorded during fetal behavioural states 1F and 2F according to Nijhuis *et al.* (1982). These behavioural states are defined as follows.

State 1F. Quiescence which can be regularly interrupted by brief gross body movements which are mostly startles, absent eye movements and a stable heart pattern with a small oscillation band-width. Isolated accelerations do occur, but these are strictly related to movements.

State 2F. Frequent and periodic gross body movements which are mainly stretches and retroflexions and movements of extremities, continuous eye movements and a heart rate pattern with a wider oscillation band-width than in state 1F and frequent accelerations during movements.

The frequency of behavioural states 3F and 4F was too low to obtain reliable blood flow velocity waveforms. In order to establish fetal behavioural states, the following variables were simultaneously recorded.

(i) The fetal heart rate (FHR), which was obtained from a Doppler ultrasound Cardiotocograph (Hewlett Packard 8040A, carrier frequency 1 MHz).

(ii) Fetal eye movements which were studied from a transverse view of the fetal face using the Diasonics CV 400 (carrier frequency 3·5 MHz).

(iii) Fetal body movements from a two-dimensional real-time linear array scanner (Toshiba Sal 20A, carrier frequency 3·5 MHz) for a sagittal view of the fetal trunk. The three transducers were placed in such a way, that there was minimal interference between the three ultrasound modes.

Flow velocity was recorded only when a clear fetal behavioural state was identified and when this state had been present over a period of ⩾3 min. All recordings were made during fetal apnoea. The maximum time for the completion of a flow velocity recording was 3 min after a behavioural state was identified.

The blood flow velocity waveforms were recorded on videotape over a 15-s period which included an average of 30 consecutive cardiac cycles. In each subject a minimum of three flow velocity waveform recordings in each vessel in each behavioural state (1F and 2F) was obtained. From hard copies of each flow velocity recording on average 20 cardiac cycles of optimal quality were selected. The degree of pulsatility of the waveform was quantified by calculating the PI according to Gosling & King (1975) using a microcomputer (Apple III). The PI changes predominantly reflect changes in peripheral vascular resistance. Since at normal fetal heart rates, changes in cardiac output are mainly regulated through changes in FHR (Kirkpatrick *et al.* 1976; Maršál *et al.* 1984), it was decided to standardize cardiac output by dividing the PI values in each subject and for each fetal behavioural state into groups, each of which representing a FHR range of 5 beats/min. This standardization will also rule out the effect of cardiac cycle length dependency of the PI when comparing PI values between behavioural states 1F and 2F. Changes in PI values with respect to the fetal behavioural state were tested using the paired Student's *t*-test. The relation between PI and FHR was tested by analysing the slopes of the individual regression lines using the Student's *t*-test.

Results

The mean number of cardiac cycles studied in the fetal internal carotid artery for all 12 subjects was 56 (range 47–68) in state 1F and 59 (range 26–76) in state 2F, a total of 1381 cycles. FHR in state 1F ranged between 109 and 164 beats/min and in state 2F between 109 and 185 beats/min. Paired analysis of the PI data in states 1F and 2F was feasible in the FHR range between 116 and 155 beats/min resulting in eight groups i.e. 116–120, 121–125, ..., 151–155 beats/min in a total number of 1160 cardiac cycles.

There was a statistically significant difference in mean PI between states 1F and 2F for all but one of the FHR ranges studied (Table 1). Figure 1 demonstrates the regression lines for the correlation between PI and FHR in states 1F and 2F for all 12 subjects. A significant reduction in PI with increasing FHR was established in states 1F ($P<0{\cdot}005$) and 2F ($P<0{\cdot}001$).

The mean number of cardiac cycles studied in the umbilical artery for all 15 subjects was 59 (range 38–82) in state 1F and 58 (range 33–76) in state 2F, a total of 1752 cycles. FHR in state 1F ranged between 105 and 185 beats/min and in state 2F between 102 and 188 beats/min. Paired analysis of the flow velocity data in states 1F and 2F was statistically feasible in the FHR range between 116 and 155 beats/min resulting in eight groups, i.e. 116–120, 121–125, ..., 151–155 beats/min in a total of 1524 cardiac cycles.

Table 2 shows a non-significant paired difference in mean PI between states 1F and 2F. Moreover, the 95% confidence interval of this paired difference displays for each FHR range a narrow distribution around zero, reflecting a virtual overlap of PI values originating from states 1F and 2F. Figure 2 demonstrates for each FHR the mean PI in states 1F and 2F for all 15 subjects studied (102–188 beats/min). An inverse relation between PI and FHR both in behavioural state 1F ($P<0{\cdot}05$) and 2F ($P<0{\cdot}001$) was established.

Discussion

Both in the human and sheep fetus cycling of behavioural patterns into identifiable states has become apparent over the last few weeks of pregnancy. Sleep state has been shown to influence cerebral blood flow in animals (Reivich *et al.* 1968), human newborn infants (Mukhtar *et al.* 1982) and adult man (Townsend *et al.* 1973), i.e. an increase has been documented during rapid eye movement sleep (active sleep) when compared with non-rapid eye movement sleep (quiet sleep). Combined two-dimensional real-time and pulsed Doppler systems allow non-invasive recording of flow velocity waveforms in the human fetal internal carotid artery. However, due to its winding path into the skull only angle-independent measurements can be made. The decrease in PI in the internal carotid artery during behavioural state 2F, as demonstrated in our study, suggests a reduction in peripheral vascular resistance in the fetal brain. Comparison of cerebral blood flow, as measured by microspheres and pulsed Doppler in young piglets (Hansen *et al.* 1983) and newborn lambs (Rosenberg *et al.* 1985), demonstrated that peak systolic and end-diastolic velocity as well as the area under the velocity curve, reflecting the shape of the waveform, closely correlate with cerebral blood flow. Since the PI is determined by all these three variables, the observed reduction in this index in the human fetal internal carotid artery under standardized FHR conditions

Table 1. Mean paired pulsatility index (PI) difference [ΔPI (1 SD)] between fetal behavioural states 1F and 2F in the FHR range between 116 and 155 beats/min in the fetal internal carotid artery in normal pregnancy

FHR range (beats/min)	No. of paired observations	Mean PI State 1F	Mean PI State 2F	ΔPI (SD)	Significance (*P*)
116–120	4	1·54	1·15	0·39 (0·23)	<0·05
121–125	8	1·58	1·20	0·38 (0·13)	<0·001
126–130	10	1·59	1·23	0·36 (0·16)	<0·001
131–135	9	1·49	1·18	0·31 (0·16)	<0·001
136–140	10	1·60	1·24	0·36 (0·21)	<0·001
141–145	8	1·54	1·19	0·35 (0·18)	<0·001
146–150	4	1·52	1·23	0·29 (0·24)	<0·10 (NS)
151–155	3	1·69	1·25	0·44 (0·17)	<0·05

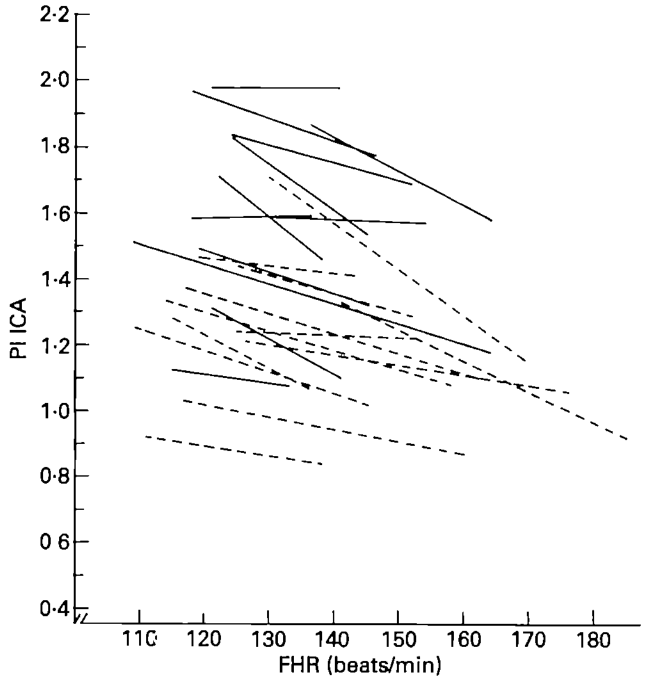

Fig. 1. Regression lines for the correlation between pulsatility index (PI) and FHR in fetal behavioural state 1F (continuous lines) and 2F (dotted lines) in the fetal internal carotid artery (ICA) for all 12 normal pregnancies.

during behavioural state 2F suggests an increase in cerebral blood flow during this state.

Of interest is the observation in the fetal lamb that there is a significant increase in cerebral oxidative metabolism during the low-voltage electrocortical state (active sleep) (Richardson *et al.* 1985) which is sustained by a rise in cerebral blood flow, which is most pronounced in the subcortex and brain stem areas (Jensen *et al.* 1985; Richardson *et al.* 1985). To determine whether a similar pattern of flow distribution is present in the human fetus we studied the flow velocity waveforms in the internal carotid artery and vertebro-basilar circulation, the latter being mainly responsible for the blood supply to the brain stem areas. Preliminary data from our unit have demonstrated that in these two cerebral vessels, reproducible flow velocity waveforms can be obtained. The possible clinical importance of flow velocity waveform recordings in

Table 2. Mean paired pulsatility index (PI) difference [ΔPI (1 SD)] and 95% confidence interval between fetal behavioural states 1F and 2F in the FHR range between 116 and 155 beats/min in the umbilical artery in normal pregnancy

FHR range (beats/min)	No. of paired observations	Mean PI		ΔPI (SD)	Significance (*P*)	95% Confidence interval
		State 1F	State 2F			
116–120	4	0·84	0·83	0·01 (0·08)	>0·20 (NS)	−0·11,0·13
121–125	9	0·83	0·83	0·00 (0·05)	>0·20 (NS)	−0·04,0·04
126–130	12	0·84	0·80	0·04 (0·08)	>0·10 (NS)	−0·01,0·09
131–135	14	0·84	0·82	0·02 (0·11)	>0·20 (NS)	−0·04,0·08
136–140	11	0·80	0·79	0·01 (0·09)	>0·20 (NS)	−0·05,0·07
141–145	11	0·79	0·76	0·03 (0·10)	>0·20 (NS)	−0·04,0·10
146–150	7	0·83	0·77	0·06 (0·09)	>0·10 (NS)	−0·02,0·14
151–155	3	0·78	0·72	0·06 (0·11)	>0·20 (NS)	−0·22,0·34

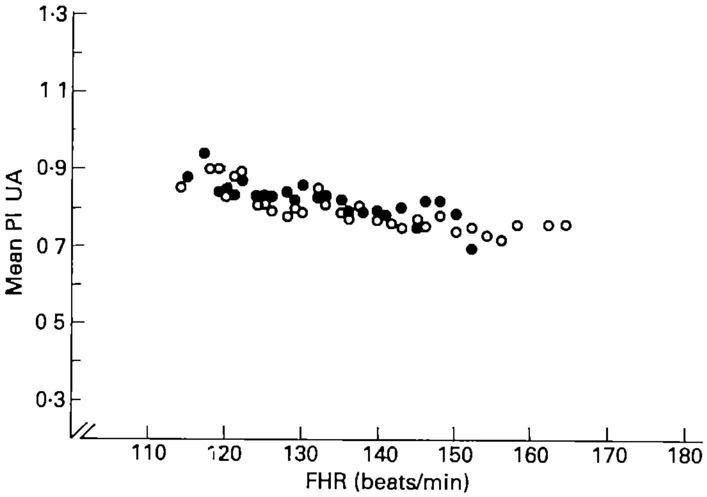

Fig. 2. Mean pulsatility index (PI) in the umbilical artery (UA) in (●) fetal behavioural states 1F and (○) 2F relative to FHR for all 15 normal pregnancies.

the human fetal internal carotid artery is based mainly on a reduction in peripheral vascular resistance in the fetal cerebrum, i.e. a brain-sparing effect in intrauterine growth retardation (Wladimiroff *et al.* 1986, 1987).

Whereas in normal pregnancies and under standardized FHR conditions, the PI in the lower thoracic part of the fetal descending aorta (van Eyck *et al.* 1985) and fetal internal carotid artery depicts significant changes with respect to the fetal behavioural state, this is not so for the umbilical artery. This independency with respect to the fetal behavioural state suggests a fetal regulatory mechanism for the state-dependent changes in the fetal descending aorta and internal carotid artery. The state independency in the umbilical artery is of practical importance since umbilical artery flow velocity waveforms can be studied in late pregnancy without taking the fetal behavioural state into account.

The decrease in PI with rising FHR observed in both the fetal internal carotid artery and umbilical artery has also been established in the fetal descending aorta both in normal and growth-retarded pregnancies (van Eyck *et al.* 1985, 1986). This inverse relation is mainly determined by the definition presented by Gosling & King (1975) for PI calculations, i.e. at a lower FHR a more gradual end-diastolic slowdown of the blood flow velocity takes place. It is essential, therefore, that when studying the effect of behavioural state on fetal blood flow, PI calculations are standardized for FHR.

It can be concluded from our data that under standardized FHR conditions there is a reduction in peripheral vascular resistance in the cerebrum during behavioural state 2F in the normal-developing human fetus, suggesting increased cerebral blood flow. The fetal behavioural state should be taken into account in further clinical studies on velocity waveforms in the fetal internal carotid artery during late pregnancy.

Acknowledgments

We are grateful to Diasonics/Sonotron for the use of the Diasonics CV 400 and the 'Drie Lichten' Foundation for their financial support of this study.

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Received 18 June 1986
Accepted 23 October 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 742–745

Doppler assessment of umbilical artery blood flow for the prediction of outcome in fetal cardiac abnormality

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Summary. In a series of 244 pregnancies referred for fetal echocardiography, the umbilical artery waveform was also studied by pulsed Doppler ultrasound. In 152 normal pregnancies diastolic flow in the umbilical artery was always detectable after 20 weeks gestation. In 4 of 58 normal patients examined before 20 weeks, diastolic flow was absent in some part of the recording. In 34 fetuses with congenital heart disease detected at between 18 and 37 weeks gestation, 10 were found consistently to have associated absent diastolic flow. Five of these fetuses died *in utero* between 5 and 21 days after the recording; three were aborted and the remaining two died in the neonatal period at 4 and 7 days after the examination. Fetal congenital heart disease with normal umbilical blood flow also had a poor prognosis in general, but the adverse outcome was much less immediate than in fetuses with absent diastolic flow. No correlation was found between the type of congenital heart disease and the characteristics of the umbilical artery waveform. Absent diastolic flow in the umbilical artery indicates a poor short-term prognosis for fetuses with congenital heart disease, particularly after 20 weeks, when fetal death is predictable.

Most of our current knowledge of the feto-placental circulation is derived from animal experiments, using methods unsuitable for studies in man (Dawes & Mott 1959; Clapp 1978).

Recently, Doppler blood velocity signals have been obtained from the umbilical artery by either continuous wave (Fitzgerald & Drumm 1977) or pulsed wave Doppler (McCallum *et al.* 1978). Audio frequency analysis of the signals yields flow velocity waveforms which contain information about cardiac and feto-placental vascular dynamics. The rate of acceleration of blood flow depends on the force of ventricular contraction, the viscosity of the blood and the elasticity of the arterial wall (McDonald 1974). The rate of the deceleration slope and the velocity at end diastole depend on the peripheral resistance, the lower the resistance the greater the velocity of diastolic flow (Olsen & Cook 1975).

The shape of the waveform will also depend on the angle between the blood flow and the Doppler beam. This effect can be removed by relating one part of the wave to the other. Many such angle independent indices have been used

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in umbilical artery waveform analysis, A/B ratio (Stuart *et al.* 1980), $\frac{A-B}{A}$ Pourcelot 1974) and the pulsatility index (PI) (Gosling & King 1975). All these indices are useful for comparison between different examinations as they reflect the feto-placental resistance. Waveform analysis has demonstrated decreasing placental resistance in normal pregnancies as gestation advances (Schulman *et al.* 1984; Trudinger *et al.* 1985; Erskine *et al.* 1985), confirming this finding in the fetal animal (Dawes 1968).

Waveforms suggestive of increased placental resistance have been recorded in intrauterine growth retardation and maternal hypertension and this has been correlated with pathological changes in the placenta (Trudinger *et al.* 1983; Giles *et al.* 1985).

We report the use of umbilical artery waveform analysis in the management of pregnancies where the fetus is known to have congenital heart disease.

Patients and methods

In a series of 244 patients referred for fetal echocardiography at between 16 and 40 weeks gestation the umbilical artery waveform was also recorded. The reasons for referral were a family history of congenital heart disease, non-immune fetal hydrops or suspected heart disease at a previous ultrasound scan. The fetal heart was examined for structural disease by cross-sectional, M-mode and Doppler echocardiography (Allan *et al.* 1982, 1984; Kleinman *et al.* 1980), using a Hewlett Packard 77020A sector scanner with a 3·5 or 5 MHz transducer.

After the cardiac study was completed, the Doppler sample volume was positioned over the umbilical cord. The Doppler gate was expanded to cover the whole cord. The umbilical artery and vein flow were obtained simultaneously where possible. The wall filter was kept to the minimum setting of 100 Hz to maximize the detection of low velocity flow. The scale was altered to display the systolic phase of the waveform on the maximum range. Recordings made during fetal breathing were not used for analysis. Systolic/diastolic ratio (A/B ratio) was determined over at least 10 cardiac cycles.

Results

In 152 normal pregnancies examined after 20 weeks gestation, the umbilical artery waveform was normal with an A/B ratio in the normal range (Trudinger *et al.* 1985; Schulman *et al.* 1984). Subsequent follow-up confirmed a normal outcome. Of 58 normal pregnancies examined before 20 weeks gestation, four showed absent diastolic flow at some point in the recording, although this was not a consistent finding if other parts of the umbilical cord were sampled.

There were 34 fetuses with congenital heart disease detected prenatally; 15 had non-immune hydrops fetalis at presentation.

Ten of these 34, including five with hydrops, had absent diastolic flow as a consistent finding in the umbilical artery. Five of the 10 fetuses were subsequently found to have chromosome anomalies; in two of them chromosome analysis was not performed. Three of these 10 pregnancies were terminated and the remaining seven fetuses all died between 5 and 21 days after the abnormal umbilical artery waveform was recorded; five were intrauterine deaths and two were neonatal deaths.

Seven of the 34 fetuses had an elevated A/B ratio. Although four of them died within 2 weeks after this recording, three remain alive 3–6 months later.

The remaining 17 pregnancies had a normal umbilical artery flow. Of these, six pregnancies were terminated because of the severity of heart disease. Although the fetus died in 9 of the remaining 11 pregnancies, in all but two, this outcome was 2–4 months after the recording was made. The exceptions were a pregnancy induced at 32 weeks for Trisomy 18 and a fetus with cardiomyopathy which responded initially to prenatal drug therapy. The infants both died shortly after delivery. The findings in all 34 fetuses with congenital heart disease detected prenatally are listed in Table 1. Table 1 shows that there is no correlation between the type of congenital heart disease and the umbilical waveform. There was no correlation either between the presence of fetal hydrops, the underlying diagnosis or the umbilical artery waveform. Under the same diagnostic heading there was a wide variation in short-term and long-term outcome.

Discussion

We feel that the addition of the umbilical artery analysis contributes important information as to

Table 1. Clinical characteristics in 34 fetuses with congenital heart disease (CHD)

Type of CHD	Gestational age (weeks)	Umbilical artery flow (UAF)	Outcome	Time between UAF and outcome
Hypoplastic left heart	18	Normal	TOP	7 days
Mitral atresia	26	Normal	TOP	3 days
AVSD+Down's	22	Normal	TOP	2 weeks
Cardiomyopathy	19	Normal	TOP	9 days
Interrupted arch	21	Normal	TOP	2 weeks
Coarctation	23	Normal	TOP	1 week
VSDs+Rh isoimmunization	28	Normal	IUD	8 weeks
AVSD+trisomy 18	32	Normal	NND	2 days
AVSD+double outlet RV	30	Normal	NND	10 weeks
Cardiomyopathy	33	Normal	NND	3 weeks
Conjoint twins	25	Normal	NND	13 weeks
Conjoint twins	24	Normal	NND	12 weeks
Coarctation	29	Normal	NND	12 weeks
Coarctation	35	Normal	NND	8 weeks
Coarctation+VSD	38	Normal	INFD	4 months
Tetralogy of Fallot (TOF)	23	Normal	A&W	6 months
TAPVD	28	Normal	A&W	6 months
Aortic atresia	32	↑ A/B ratio	IUD	2 weeks
Coarctation	22	↑ A/B ratio	IUD	2 weeks
AVSD+trisomy 18	37	↑ A/B ratio	NND	2 weeks
Mitral atresia	37	↑ A/B ratio	NND	2 days
AVSD+Down's	34	↑ A/B ratio	A&W	6 months
AVSD	32	↑ A/B ratio	A&W	3 months
Double outlet RV	33	↑ A/B ratio	A&W	6 months
Coarctation+xo	20	Absent dias flow	TOP	6 days
AVSD+exomphalos	26	Absent dias flow	TOP	10 days
TOF+exomphalos	24	Absent dias flow	TOP	4 days
Cardiomyopathy	32	Absent dias flow	IUD	5 days
AVSD+Down's	32	Absent dias flow	IUD	21 days
Coarctation+trisomy 18	31	Absent dias flow	IUD	14 days
AVSD	18	Absent dias flow	IUD	16 days
Tetralogy of Fallot	28	Absent dias flow	IUD	10 days
Hypoplastic left heart	33	Absent dias flow	NND	7 days
Ebstein's anomaly	37	Absent dias flow	NND	4 days

TOP, Termination of pregnancy; IUD, intrauterine death; NND, neonatal death; INFD, infant death; A&W, alive and well; AVSD, atrioventricular septal defect; TAPVD, total anomalous pulmonary venous drainage, Dias, diastolic.

the short-term outcome in the individual case. Absent diastolic flow indicates a poor immediate outcome whatever the type of congenital heart disease. This can allow interruption of pregnancy where this is found earlier than 28 weeks gestation. When the diagnosis is made in late gestation, the mother can be prepared for a poor postnatal outcome. Alternatively, where the heart disease is amenable to medical or surgical therapy, early delivery may save a fetus which would otherwise die *in utero*.

It is possible to postulate that the abnormal umbilical artery waveform is a result of low cardiac output in these fetuses with congenital heart disease, although a low cardiac output is uncommon in congenital heart disease, even in severe cardiac failure. The exception to this would be cardiomyopathy. Of our three fetuses with cardiomyopathy, two were documented as having a severely reduced cardiac output and yet one of these retained normal umbilical flow. Similar forms of congenital heart disease are associated with normal and abnormal waveforms. Abnormal chromosomes in the fetus also did not produce a consistently abnormal waveform, although there was a greater proportion of fetuses with abnormal chromosomes and abnormal waveforms than otherwise.

Two previous authors have reported abnormal placental flow in pregnancies with major fetal anomaly (Trudinger & Cook 1985; Nyland *et al.* 1983). They suggest a primary fetal mechanism triggering a placental vascular lesion. Whatever the mechanism for abnormal umbilical blood flow velocity waveforms, the Doppler examination of the umbilical artery, which is a quick and easy recording to make, has useful prognostic value in the management of pregnancies complicated by fetal abnormalities.

Acknowledgment

L.D.A., D.C.C. and S.K.C. are supported by the British Heart Foundation. W.Al-G. is supported by the Iraqi Government.

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Received 5 August 1986
Accepted 26 January 1987

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 746–752

Management of the mature selected breech presentation: an analysis based on the intended method of delivery

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Summary. The outcome of 313 mature singleton breech deliveries, covering a 3-year period at the Queen Charlotte's Hospital, is reviewed. Maternal and fetal outcome were analysed by the intention to deliver vaginally compared with planned caesarean section. There was no serious fetal morbidity or mortality in either of these groups despite considerable mechanical difficulty with vaginal delivery of the head in one patient. One woman in this group required hysterectomy for haemorrhage after an emergency caesarean section. Planned caesarean sections were carried out in 125 cases (40%). Trial of vaginal delivery was abandoned in 59 (40%) of the 149 women where this was attempted. Epidural analgesia appears to increase the duration of the second stage of labour in those who were delivered vaginally. Younger women and those with smaller babies were more likely to succeed with a trial of vaginal delivery but there was no relation between birthweight and the radiological obstetric conjugate and success or failure of trial of labour.

Elective caesarean section for breech presentation was suggested by Soni (1931) and has become the standard management for many obstetricians. Recently encouraging results have been reported for vaginal delivery of carefully selected cases and this has been followed by a swing away from routine elective surgery. Over 20 series of breech presentation have been reported in the last decade. With five exceptions (Anderman *et al.* 1984; Collea *et al.* 1980; Gimovsky *et al.* 1983; Jaffa *et al.* 198[illegible]; Watson & Benson 1984), these papers compare caesarean section with vaginal delivery. This is an unhelpful comparison since the primary decision concerns planned caesarean section versus a trial of vaginal delivery. Thus patients undergoing caesarean section include both those allocated for elective delivery and those who required a caesarean section where vaginal delivery was intended. The failure of many authors to distinguish these two events prompted us to review practice over 3 years in our hospital, noting neonatal and maternal outcome after both treatment strategies.

Patients and methods

The records of all singleton breech deliveries from 1982 to 1984 inclusive were reviewed. Only breech deliveries of 36 weeks gestation or over were included. Cases where the breech presentation had been diagnosed in the antenatal clinic were classified by the intention to carry out caesarean section (planned caesarean delivery) or to conduct trial of labour. Similarly, patients where the breech was first diagnosed in labour were classified into those that were managed by immediate caesarean section and those in whom a trial of labour was allowed. Those assigned for elective

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caesarean section but who presented in labour before the date assigned for operation were noted. Along with details of the delivery, details of complications to hospital discharge were extracted from the patient records.

The usual criteria for vaginal delivery in our hospital are listed in Table 1. From a detailed review of the notes it was clear that these criteria were not followed for every patient assigned to a trial of vaginal delivery and a record was kept of such patients. X-ray pelvimetry is performed on most patients before deciding on a trial of vaginal delivery. In our hospital only erect lateral pelvimetry is performed because it is felt that the increased amount of information gained from full X-ray pelvimetry does not justify the increased dose of radiation to the fetus (Gimovsky *et al.* 1985). Similarly a specific search for hyperextension of the fetal neck was not made.

The majority of breech vaginal deliveries and caesarean sections in our hospital are managed with epidural analgesia. Labour is monitored by continuous cardiotocography. Vaginal delivery is by assisted breech delivery with elective application of forceps to the aftercoming head.

We were able to compare some of our results with a published series from the same hospital covering the years 1971–1972 (Bowen-Simpkins & Fergusson 1974).

Results

Prevalence of breech delivery

During the years 1982–1984 inclusive, 12 462 deliveries took place. Excluding twins, there were 313 mature breech presentations (a rate of 2·5%).

Table 1. Criteria used in defining a selected group of breech presentations at low risk from vaginal breech delivery

1. Estimated fetal weight 2·5–4 kg (usually on the basis of ultrasound examination and clinical judgement)
2. Frank breech presentation
3. Inlet, midcavity and outlet >11 cm on erect lateral pelvimetry and no encroachment on cavity detected on clinical examination
4. No serious medical or obstetric complications
5. Fetal abnormality excluded as far as possible by ultrasound

Congenital abnormalities

There were three neonatal deaths in the series. All were due to lethal congenital abnormalities that had been diagnosed antenatally. Two infants had a lumbar meningocele with hydrocephalus and one had an isolated hydrocephalus.

There were seven further major congenital abnormalities (two intersex, two talipes, limb defect, cranial abnormality and cystic fibrosis). This provides an overall rate of major congenital abnormalities of 3·5% (11 of 313).

Method of delivery

Vaginal delivery was attempted in 149 women (48%) and 90 of them were delivered vaginally; the trial failed in 59 (40%) and they were delivered by caesarean section. When only the 85 women who fulfilled all the selection criteria in Table 1 are considered, then 51 (60%) were delivered vaginally and the trial failed in 34 (also 40%). Planned caesarean section was performed in 125 and the other 39 women were delivered by caesarean section as soon as they arrived in the labour ward. These 39 women included 32 who presented in labour before the date assigned for their elective caesarean section and seven patients in whom the breech was not diagnosed before labour and for whom vaginal delivery was felt to be contraindicated. Table 2 details the mode of delivery by parity in the 313 patients.

For the remainder of this report patients in whom a trial of vaginal delivery was attempted will be referred to as the 'trial-of-vaginal-delivery group'. Patients who underwent elective caesarean section or caesarean section as soon as they arrived on the labour ward will be referred to as the 'planned-section group'.

Outcome by Apgar score

Excluding congenital abnormality, 1-min Apgar scores were statistically significantly lower in patients who underwent trial of vaginal delivery (Table 3). This applies even if cases where general anaesthesia was used are excluded. All significant differences had, however, disappeared at 5 min at which time there were no babies with Apgar scores of <5 in either group.

Table 2. Mode of delivery in 313 mature singleton breech presentations by parity

Mode of delivery	Primiparae	Multiparae	Total
Vaginal delivery attempted ($n = 149$)			
Vaginal delivery achieved	57 (28)*	33 (23)*	90 (51)*
Section in labour	46 (27)*	13 (7)*	59 (34)*
Caesarean section planned ($n = 164$)			
Elective section before labour	84	41	125
Section as soon as possible after onset of labour	29	10	39

*The number in parenthesis shows the patients who fulfilled all criteria in Table 1.

Fetal morbidity noted until discharge

There were no serious fetal complications in either group. Three babies were described as jittery in the trial-of-vaginal-delivery group and one in the planned-section group. There was one fractured clavicle following vaginal delivery and one laceration of the buttock following an elective caesarean section.

Maternal complications

There were no maternal deaths. There was only one serious maternal complication in that a patient delivered by caesarean section after a failed trial of vaginal delivery developed uncontrollable bleeding and required a hysterectomy. In another woman, emergency endotracheal intubation for anaesthesia after a failed trial of vaginal delivery proved impossible, but aspiration did not occur during the delivery by caesarean section under general anaesthesia.

Difficulties with the aftercoming head

Difficulty with the birth of the aftercoming head was recorded in 2 of the 90 women delivered vaginally. In one woman the head was stuck for 6 min and a considerable amount of manipulation and suprapubic pressure was required to effect the birth. Remarkably, the baby was born in good condition and there was no subsequent morbidity.

Experience of epidural analgesia in trial of vaginal delivery

The methods of delivery for patients with and without epidural analgesia assigned to a trial of labour are shown in Table 4. This is compared with results from the same hospital covering the years 1971–1972 (Bowen-Simpkins & Fergusson 1974). The results demonstrate a greater readiness to perform caesarean section and reluctance to carry out breech extraction in the present

Table 3. Apgar score by method of management

	Planned section		Trial of vaginal delivery	
1-min Apgar score	Epidural	General anaesthesia	Epidural	General anaesthesia
1			3	
2			5	
3			5	1
4	2	5	11	
5	3	2	13	
6	14		13	
7	13	2	16	1
8	40	6	44	
9	61	3	36	
10	10		1	

Apgar scores were significantly lower in the trial-of-vaginal-delivery group, both overall (2-tailed Mann–Whitney *U*-test $P<0{\cdot}0001$) and also excluding the patients managed with general anaesthesia. (Mean rank 172 planned caesarean group cf 119 in vaginal trial group: 2-tailed P again $<0{\cdot}0001$). The difference between groups had disappeared at 5 min.

Table 4. Method of delivery in patients undergoing trial of vaginal delivery with and without epidural analgesia compared with results from the same hospital between 1971 and 1972*

	Present series (1982–1984)		Previous series* (1971–1972)	
Method of delivery	Epidural	No epidural	Epidural	No epidural
Assisted breech	72	16	57	49
Groin traction	2	0	7	4
Extraction	0	0	2	6
'Failed' trial (delivered by caesarean section)	50 (40%)	9 (36%)	6 (8%)	2 (3%)
	124	25	72	61

*From Bowen-Simpkins & Fergusson (1974).

series, but it should be noted that two neonatal deaths resulting from birth injury occurred in the previous series, compared with none in the present.

In the 1971–1972 series the difference in the duration of the second stage in patients with and without epidural analgesia only just reached statistical significance ($P = 0{\cdot}05$). In the present series, patients with epidural analgesia had significantly longer second stages of labour than either group of patients in the previous series (Table 5).

The duration of active pushing for patients with epidural analgesia was considerably less than that of the second stage as a whole. This information was recorded for 60 of the 72 patients; 22 of these pushed for <30 min , 25 for 30–60 min and 13 for >60 min. One of these patients pushed for >120 min.

Reasons for failure of trial of vaginal delivery

These are detailed in Table 6, where it can be seen that poor progress is much the commonest indication for a non-elective caesarean section. Labour was induced in 47 of the 149 women (31%) in the trial-of-vaginal-delivery group, 28 of them were delivered vaginally and the other 19 by caesarean section after the trial failed. Oxytocin was used in 48% of failed trials of labour following epidural analgesia. It is noteworthy that 29 of the 59 (49%) failed trials of labour occurred in the second stage.

Relation between birthweight and obstetric conjugate and method of delivery

X-ray pelvimetry was carried out in 126 of the 149 patients who were managed by trial of vaginal delivery. We found no relation between birthweight and obstetric conjugate and method of delivery (mean conjugate of those giving birth vaginally = 12·7 cm (SE 0·11); mean conjugate of those requiring a section in labour = 12·8 cm (SE 0·12)). Of the patients in the planned-section group, 75 had pelvimetry and in 40 of them reduced pelvic dimensions were given as the indication for elective delivery.

Outcome for breech presentation diagnosed in labour

We were surprised and disappointed to find that 29 of the 313 breech presentations (9%) were diagnosed for the first time in labour. Vaginal delivery was achieved in 13 of these women; in 9 of them a trial of vaginal delivery was attempted but ended in caesarean section. Seven patients were deemed unsuitable for vaginal delivery and they were delivered by caesarean section as soon as possible.

Maternal age and method of delivery

Of the 313 women, 185 were under 30 years of age, and 128 were over 30; 45 patients were over the age of 35. Vaginal delivery was attempted less frequently after the age of 30 (39% compared with 53%) and, where it was attempted, was more likely to lead to caesarean section. Thus 50% of patients over the age of 30 required cae-

Table 5. Length of recorded second stage for assisted vaginal breech delivery

Duration of second stage (min)	Present series (1982–1984)		Previous series (1971–1972)	
	Epidural ($n = 72$)	No epidural ($n = 16$)	Epidural ($n = 55$)	No epidural ($n = 48$)
0–29	15	14	16	26
30–59	12	2	20	14
60–89	12		11	7
90–119	11		5	1
>120	22		3	0
χ^2	$P = 0{\cdot}000003$*		$P = 0{\cdot}05$	

*It is suggested that this difference is due to both the effect of epidural analgesia and a greater readiness to perform breech extraction in the earlier series.

sarean section after failed trial of labour compared with 34% in the younger age group.

Birthweight and method of delivery

Women with large fetuses, like those who are older, are less likely to be given a trial of vaginal delivery and trials fail more frequently. Thus trial of labour was attempted in 41% where the baby weighed >3500 g and in 49% where fetal weight was less than this. Trial of labour was successful in 36% of those with babies weighing over 3500 g compared with 66% where the baby weighed less.

Discussion

Various authors have advocated trial of vaginal breech delivery for patients selected by defined criteria (Collea *et al.* 1980; Gimovsky *et al.* 1983; Jaffa *et al.* 1981; Tatum *et al.* 1985; Watson & Benson 1984). None of these authors gives an estimate of how many of a general population of term breech presentations would be selected by their criteria. The criteria listed in Table 1 are broadly in line with those suggested by other authors, although some include non-frank breech presentations, some have a reduced upper limit for estimated fetal weight and most have radiological criteria for transverse pelvic measurements (as explained in methods, we only employed erect lateral pelvimetry to reduce the dose of radiation to the fetus). We found that only 85 of our 313 breech presentations fulfilled all selection criteria. A further 10 fitted all criteria, but pelvimetry was not performed because the patient requested a caesarean section whatever the result. Thus approximately one third of our consecutive series of mature breech presentations were selected by our defined criteria. A similar calculation can be performed on the data of Watson & Benson (1984), by whose criteria (in which non-frank breech presentations are excluded) 91 patients were selected from a total population of mature breech presentations of 254 (44%). The only other series giving data for this

Table 6. Analysis of failure of vaginal trial

Variable	Primiparae	Multiparae	Total
Fetal distress in first stage	4	0	4
No progress in first stage	13 (12,5)*	5 (4,2)	18
Fetal distress in second stage	4	2	6
No progress in second stage	18 (18,13)*	5 (5,2)*	23
Failed induction	6	0	6
Cord prolapse	0	1	1
Flexed converted to footling	1	0	1
	46	13	59

*Number of epidurals in labour followed by number of cases where oxytocin augmentation was employed.

calculation is that reported by Jaffa *et al.* (1981). These authors do not take the type of breech (frank, complete or footling) into account and found 277 out of 321 (86%) mature breech presentations were suitable for trial of vaginal delivery. In view of this wide range in the proportion of cases deemed suitable for vaginal delivery, we suggest that studies advocating a trial of vaginal delivery for selected cases should quote the proportion of the general population of breech presentation selected by their criteria.

Our rate for failed trial of vaginal delivery was high, 59 out of 149 (40%), and represents a marked increase over the rate of 6% (8/133) for a series from the same hospital covering the years 1971 and 1972 (Bowen-Simpkins & Fergusson 1974). The reasons for failed trial in the present series are analysed in Table 6 where it can be seen that poor progress, despite frequent use of oxytocin, is the commonest indication for a non-elective caesarean section. A greater readiness to resort to caesarean section and the more frequent use of epidural analgesia are probably the most important factors accounting for the increased rate of failed trials. It should be noted that two neonatal deaths resulting from birth injuries following vaginal delivery occurred in the previous series, compared with none in the present.

The higher the rate of failed trial of labour, the less desirable a policy of allowing a trial of vaginal delivery becomes (Bingham & Lilford 1987). This is because the risks of emergency caesarean section are greater than those of elective operations (DHSS1986; Patek & Larsson 1978; Nielson & Hokegard 1983; Feldman & Freiman 1985). These risks may be even greater if the patient is in the second stage of labour (one half of intrapartum sections in our series). Our only serious maternal morbidity was associated with a failed trial of labour and the patient required a hysterectomy to control intra-operative haemorrhage. Many breech series do not give rates for failed trial of labour (Confino *et al.* 1985*a,b*; Petitti & Golditch 1984; Schutte *et al.* 1985; Tatum *et al.* 1985) and this is obviously an important piece of information. Reported rates for failed trials are by Anderman *et al.* (1984), 30/76 (39%); Gimovsky *et al.* (1983), 11/42 (26%); Watson & Benson (1984), 22/69 (24%) and Collea *et al.* (1980), 11/49 (18%).

In the present study we compared 1-min Apgar scores by the intended method of delivery, excluding lethal congenital abnormality, and found these were lower after trial of vaginal delivery. This difference remains after exclusion of patients delivered under general anaesthesia, which may have artificially further depressed Apgar scores in the caesarean section group. The difference in Apgar scores at 1-min was not present after 5 min. Whereas a 1-min Apgar score correlates very poorly with subsequent neurological outcome, our finding of low Apgar scores in patients where a vaginal delivery was attempted tends to confirm that vaginal breech delivery may be an asphyxiating process. No serious infant morbidity was noted to discharge, although a recent review of the literature suggests that lethal or permanently disabling conditions may occur in about 8 in 1000 trials of mature vaginal breech delivery excluding congenital abnormalities.

Surprisingly, four series of breech presentation (Bowen-Simpkins & Fergusson 1974; Breeson *et al.* 1978; Crawford 1974; Crawford & Weaver 1982) have shown no increase in breech extraction and emergency caesarean section when epidural analgesia was employed. Epidural analgesia has, however, been shown to increase the forceps delivery rate in vertex presentation (Studd *et al.* 1980, 1982). The reason for the greatly prolonged second stage with epidural analgesia in this series may reflect a greater willingness to wait for the breech to descend before encouraging expulsive efforts. Unfortunately, we do not have a large enough control group to demonstrate any association between epidural analgesia and the rate of breech extraction and emergency caesarean section. We have shown that diagnosis of breech presentation in labour, maternal age and birthweight affect the outcome of trial of labour and the distribution of these variables should be taken into account when making a detailed comparison between breech series. In contrast to Joyce *et al.* (1975) we found no relation between maternal obstetric conjugate and the outcome of a trial of vaginal delivery. Our findings are in agreement with Jagani *et al.* (1981) who also failed to find a relation between pelvic measurements, birthweight and outcome in trial of vertex vaginal delivery.

Detailed retrospective examination of hospital case notes, as in this study, may serve as a form of audit from which others may benefit. In this analysis it was apparent that a number of patients underwent unnecessary X-ray pelvimetry as elective caesarean section was carried out despite radiological demonstration of adequate pelvic dimensions. As fetal exposure to X-rays may predispose to childhood leukaemia, this investigation should only be performed if all other criteria for trial of vaginal delivery have been found to be satisfactory.

In conclusion, we have shown that breech delivery, including trial of vaginal breech delivery, is now much safer than it was, even in the same hospital, 10 years ago. However, it appears that this added safety has been achieved at the expense of a much higher planned and, more importantly, intrapartum caesarean section rate. The latter, in particular, reduces the utility of trial of vaginal delivery for the mother and many doctors and their patients will have to take this into account in deciding on the management of breech delivery.

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Received 22 July 1986
Accepted 23 December 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 753–757

Maternal posture in second stage and fetal acid base status

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Summary. The effect of position during the second stage on outcome was studied in 58 women, with no exclusions because of pregnancy complications or signs of fetal distress, who were randomly allocated to have the second stage conducted in either the dorsal or 15° lateral tilt position. All the women were of parity 0 or 1 and the two groups were well matched except for gestational age at delivery. There were no differences in clinical outcome between the two groups, but overall the dorsal group had lower cord artery pH values ($P<0{\cdot}05$), higher $P\text{co}_2$ ($P<0{\cdot}01$) and a greater base deficit, but not significantly so. pH and base deficit were similar in both groups where the second stage did not last >15 min. Thereafter, there was a trend to decreasing pH and increasing base deficit with increasing length of second stage in the dorsal group, but not in the tilt group though this did not reach statistical significance. Low Apgar scores, complicated pregnancy and first pregnancy were each associated with significantly lower pH levels. Prolonged placement of the patient in the flat dorsal position should be avoided in second stage, though a suitable alternative under the conditions described has not been defined.

In late pregnancy the flat dorsal position reduces placental perfusion by an average of 25% compared with the lateral position (Kauppila *et al.* 1980) and is well recognized to predispose to fetal heart rate decelerations in labour. While semi-sitting positions are perhaps most common, it has become very uncommon for women in hospitals in the developed world to give birth while lying flat on their backs. As Cohen (1983) concluded, 'few today would advocate the use of the supine position during the second stage'.

Conditions are quite different in many countries in the world, where the midwife may have to look after several labouring women without the support of an assistant or husband, and where the supine position remains the standard one for the expulsive phase of labour. The question of whether this really matters for the short duration of second stage is an important one; if it is harmful, then very large numbers of babies are at risk; if it is not, then major changes in current practice need not be introduced on this account.

This has been studied twice by randomized controlled trial. Humphrey *et al.* (1973) compared the dorsal and 15° lateral tilt positions in 40 women during the second stage. Although no significant differences in umbilical artery pH were found in that study, a reanalysis of the data (Humphrey *et al.* 1974) showed the regression line of fall in pH with duration of second stage to be statistically significant in women in the dorsal group who were delivered within 30 min, but not in the tilt group. It is difficult to reconcile the

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Table 1. Characteristics of pregnant women and babies studied

	Back	15° Tilt
n	30	28
Age (years)	24·7 (4·1)	25·0 (5·8)
Parity	0·40 (0·49)	0·43 (0·49)
Length of first stage (hours from admission)	6·0 (3·7)	6·9 (3·1)
Gestation (completed weeks)	40·1 (1·5)	39·1 (1·6)*
Birthweight (g)	3379 (475)	3210 (662)
Birthweight <5th centile (*n*)	3	4
Severe proteinuric pre-eclampsia (*n*)	1	1
Other hypertensive disease (*n*)	1	5
Meconium stained amniotic fluid (*n*)	9	4
Gestation more than 14 days past term (*n*)	4	1

Results are means (SD) where appropriate.
* Significance of difference between the two groups $P<0{\cdot}05$, $t = 2{\cdot}41$

Table 2. Clinical outcome

	Back	15° Tilt
n	30	28
Length of second stage (min)	26·3 (16·9)	24·0 (13·4)
Mode of delivery (*n*)		
Vacuum or forceps	5	4
Caesarean section (cs)	1	0
1 min Apgar score	8·0 (1·1)	8·0 (1·1)
Number with 1-min Apgar score <7 (*n*)	8	6
Number with 5-min Apgar score <7 (*n*)	1	0
Oxygen resuscitation with face mask	5	3
Episiotomy	25	24
Blood loss (ml) (excluding CS)	246 (77)	279 (118)

Results are means (SD) where appropriate.
No difference was statistically significant.

clear effect in those delivered within 30 min with the absence of effect in births that took twice as long. Another trial by Stewart *et al.* (1983) did not support this finding. In that study 189 deliveries were conducted either in a birth chair or in the dorsal position. Even though a high proportion had epidural analgesia, the condition of the baby at birth was said to be similar in the two groups, though no data were given.

Thus, though there are sound theoretical reasons why the flat dorsal position may be undesirable there is little evidence that it is so in practice. We felt this fundamental and important issue should be resolved and planned a study along the lines of Humphrey *et al.* (1973) but under very different conditions.

Patients and methods

The study was performed in the Maternity Hospital, Kuwait. This is a very busy referral unit, with a great concentration of pregnancy and labour complications, and 18 000 deliveries per year. Each midwife looks after up to four labouring women, and as she tends to glove and prepare for delivery when pushing starts, it is difficult for her to listen to the fetal heart frequently. The second stage is almost always conducted with the patient lying completely flat on her back (Johnstone *et al.* 1987). Only women of parity 0 or 1 were included in this trial because most patients of higher parity gave birth so rapidly that it was unlikely that any effect of change in posture could be demonstrated. These parity groups were randomized separately, to give more in the nulliparous group. Other than this, women were selected only on the basis that they did not need immediate delivery and that they agreed to participate. Approval for the study was given by the ethics committees of the University of Kuwait and Ministry of Health.

After recruitment, at the onset of second stage, women were allocated randomly to the dorsal or tilt groups. This was done using sealed envelopes kept on the labour ward. For the

Table 3. Acid base status related to position

	Back	15° Tilt	Statistical significance
n	30	28	
pH	7·19 (0·10)	7·24 (0·06)	$t = 2{\cdot}30$ $P<0{\cdot}05$
$P\text{CO}_2$ (mmHg)	61·43 (13·15)	53·72 (7·71)	$t = 2{\cdot}70$ $P<0{\cdot}01$
$P\text{O}_2$ (mmHg)	20·45 (12·66)	19·35 (8·82)	NS
Base deficit (mmol/l)	6·98 (3·69)	5·60 (2·84)	NS
Bicarbonate (mmol/l)	21·90 (2·30)	22·18 (2·63)	NS

Results are means (SD).

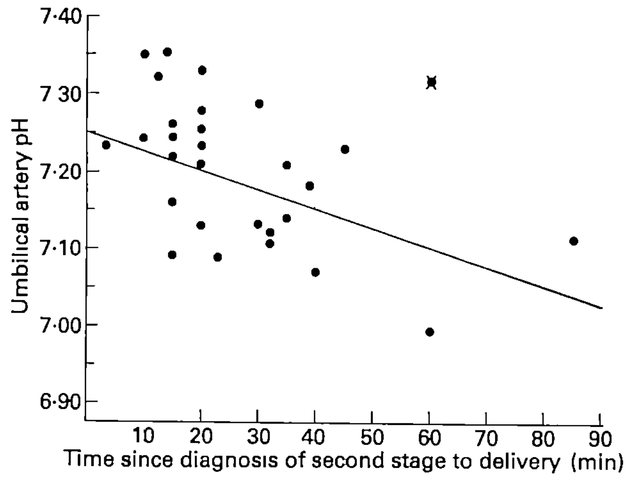

Fig. 1. Flat dorsal group, pH and duration of second stage ($r = -0{\cdot}42$, $P<0{\cdot}05$). The patient circled was the only patient to be delivered by caesarean section, and the only patient where length of second stage was not recorded. Second stage has been arbitrarily drawn at an hour in the figure, but not included in the correlation

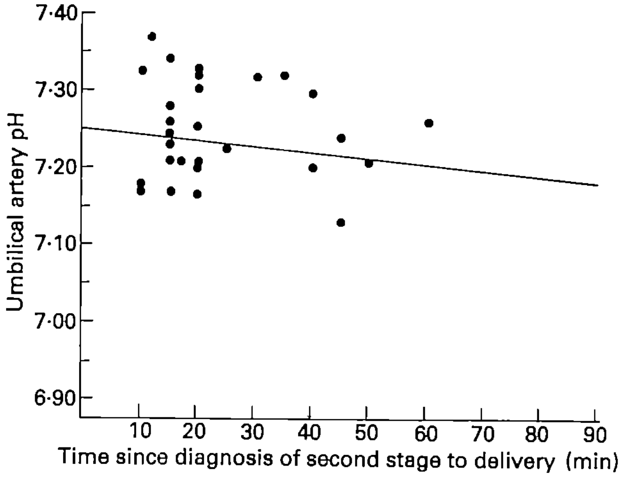

Fig. 2. 15° tilt group, pH and duration of second stage ($r = -0{\cdot}10$, NS). See also Fig. 1

latter group, 15° lateral tilt was achieved by putting a firm pillow or towels under the right hip. The conduct of the second stage and delivery was left to the care of the midwife and attending doctors. Immediately after delivery the cord was double clamped, and a 2 ml blood sample was aspirated from the umbilical artery into a plastic syringe which had been flushed with 1000 units/ml of heparin solution. This sample was immediately analysed on an ABL-2 analyser (Radiometer, Copenhagen, Denmark) kept on the labour ward.

All obstetric details, including length of second stage, were recorded at the time on a special sheet, and the gas analyser print-out, together with the randomization card, were stapled to this sheet. Statistical analysis was done using Student's *t*-test for the comparison of means and analysis of variance.

Results

The number of women randomized was 61, but one patient in each group had no fetal gas analy-

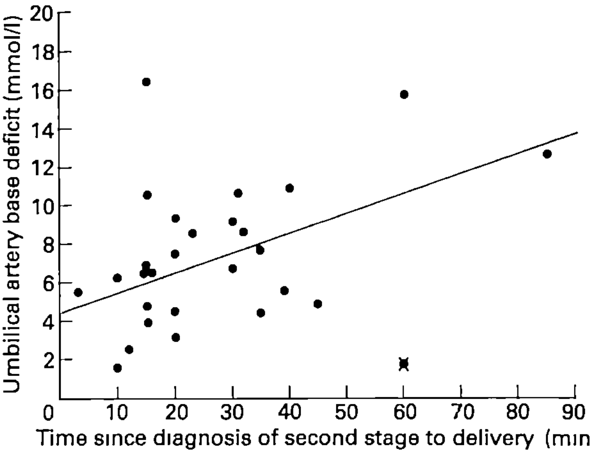

Fig. 3. Flat dorsal group, base deficit and duration of second stage (r = 0·48, P<0·01). See also Fig. 1 The case circled was not included in the correlation

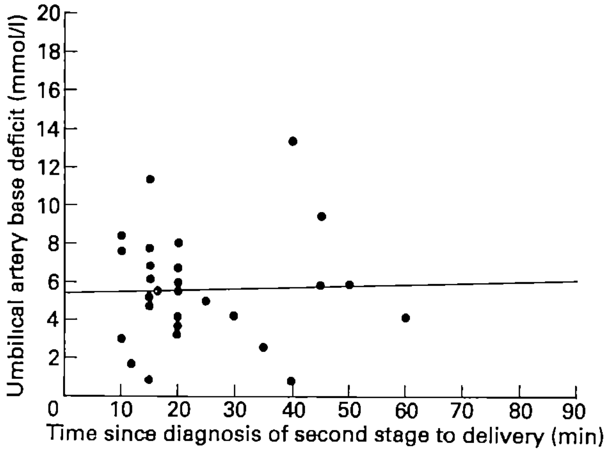

Fig. 4. 15° tilt group, base deficit and duration of second stage (r = 0·03, NS) See also Fig. 1.

sis attached to her data sheet, and one had an obviously incorrect blood gas result. Table 1 shows the clinical characteristics of the remaining 58 women. There were many risk factors, but the only statistically significant difference between the two groups was in length of gestation which was earlier in the tilt group (P<0·05). No patient had epidural analgesia but 64% of women had pethidine (mean throughout labour for these women 120 mg) and 40% were given oxytocin. There were no significant differences in administration of pethidine or oxytocin between groups.

There were no obvious advantages to either group in length of second stage, need for operative delivery, and condition of the baby as judged either by Apgar score, or need for resuscitation (Table 2).

Table 3 shows that compared with the tilt group the dorsal group has a lower pH (P<0·05) and a higher $P\text{CO}_2$ (P<0·01). The base deficit is greater but not significantly so. From Figures 1–4 it can be seen that pH and base deficit are similar in both groups where the second stage does not last >15 min, but that there is a trend to deterioration with increasing length of second stage in the dorsal group (r = −0·42, P<0·05 and r = 0·48, P<0·01 for pH and base deficit respectively) but not in the tilt group (r = −0·10, NS and r = 0·03, NS respectively).

Overall, significantly lower pH values were found in babies with lower Apgar scores, in first born babies and in association with complications of pregnancy or labour.

Discussion

This study suggests that lying flat in the dorsal position for even the short duration of second stage does lower fetal artery pH and that this may be worse the longer the second stage. This is rather different and more emphatic than the one previous study examining this (Humphrey *et al.* 1973, 1974) though the conditions are different. It is, however, compatible with previous observations of a fall in fetal pH during the second stage (e.g. Weber & Hahn-Pederson 1979), some of which may be due to position, the results are in the same range as reported by most others who have not excluded abnormal cases (e.g. Sykes *et al.* 1982) and the data do show internal consistency. Clearly, most babies come to no clinical harm but, in the absence of close fetal monitoring, it is possible that babies already in poor condition, or babies where delivery is difficult or prolonged, may suffer additionally as a result, and it is also possible that a small percentage of women are particularly at risk.

Where the second stage is short, position probably does not matter, but we agree with Humphrey *et al.* (1974) that 'prolonged placement of the patient in the dorsal position appears inadvisable'. However, the 15° lateral tilt position is a nuisance for midwives and not particularly comfortable for patients, and semi-sitting positions are difficult for an unaided midwife without a specially designed bed. We therefore plan to study the feasability of alternative positions under the conditions described where the second stage lasts longer than 15 min.

Acknowledgments

This work was supported by grant no. MDO 130 from Kuwait University. We are very grateful to Mrs Pamela Warner, of the MRC Reproductive Biology Unit in Edinburgh, for statistical advice. We are also very grateful to Dr Aly D-El-Tannir, Director of the Maternity Hospital, for his help.

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Received 6 May 1986
Accepted 26 November 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp 758–764

Cortisol and loss of malaria immunity in human pregnancy

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Summary. The concentration of both total (bound to corticoid-binding-globulin plus free) and free cortisol was determined in sera from two groups of pregnant women in Tanzania. One group consisted of 152 pregnant women (57 nulliparas and 95 multiparas) exhibiting clinical malaria during pregnancy, and the other group comprised 527 pregnant women (105 nulliparas and 422 multiparas), who did not have a record of malaria during pregnancy. The serum concentration of total cortisol was significantly higher in women with clinical malaria than in women without recorded malaria, and this is true for both nulliparae and multiparae. Free cortisol fractions did not differ significantly between these groups. Indications were obtained that higher total cortisol levels cause loss of malaria immunity rather than being concomitant with malaria infection only. The data are compatible with those of a murine malaria model.

Malaria morbidity and mortality is higher in pregnant women than in non-pregnant women (Gilles *et al.* 1969; Bruce-Chwatt 1983). Even women living in holoendemic areas who are supposed to be protected by their immunity against severe malaria suffer the hazardous effects of repeated malaria attacks during pregnancy (Kortman 1972), particularly during first pregnancy.

The higher prevalence of not only malaria parasitaemia (Campbell *et al.* 1980) but even clinical malaria during pregnancy (Kortman 1972; Vleugels 1984) is presumed to express loss of a previously established immunity. Gestational changes in immune responsiveness usually are cell-mediated rather than humoral responses (Fabris *et al.* 1976).

The serum concentration of cortisol increases linearly during pregnancy (Vleugels 1984) and is higher in nulliparas than in multiparas (Vleugels *et al.* 1986).

These observations together with an observed relation between changes in serum corticosterone and loss of malaria immunity during pregnancy in mice (van Zon *et al.* 1982, 1985*a*) prompted the analysis of changes in serum cortisol levels in relation to occurrence of clinical malaria in human pregnancy.

Subjects and methods

Two study groups were formed. The first group consisted of 152 pregnant women (57 nulliparas

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and 95 multiparas) who exhibited clinical malaria during pregnancy (malarious group). The second group consisted of 527 pregnant healthy women (105 nulliparas and 422 multiparas), who did not exhibit malaria during their pregnancy (non-malarious group). All these women visited the antenatal clinics of the rural Turiani Hospital in Tanzania in the period between February 1981 and May 1982.

Gestational age was derived from the fundal height and the history of amenorrhoea and recorded in an even number of weeks.

Blood samples were collected by venous puncture. Since the serum cortisol concentration exhibits diurnal variation all samples were collected between 11.00 hours and 13.00 hours, while patients were in a sitting position. Blood samples were stored in a refrigerator for about 2 h and then centrifuged (1000 r/min) for 10 min. Serum was separated and stored at −20 °C, transported by air in a frozen condition to Nijmegen, The Netherlands, and again stored at −20 °C until analysed.

Total serum cortisol. Concentrations were determined with the AUTO-PAK cortisol test kit system (MICRO-MEDIC Systems). The test consists of a quantitative radioimmunoassay for the determination of cortisol in human serum, using cortisol-iodine 125-histamine as tracer. Rabbit antibodies raised against cortisol were fixed to test tubes as the solid phase. The tests were run in the fully automated CONCEPT-5 (MICRO-MEDIC Systems). The sensitivity of this radioimmunoassay was 0·1μg/dl at 95% B/B_0 (B, actual binding; B_0 initial binding). The data exhibited an inter- and intra-assay coefficient of variation of 5·1% and 4·5% respectively, as has been described earlier (Vleugels *et al.* 1986). All the measurements were made with a mean maximum binding of 27·8% (SD 5%).

Free cortisol fraction. These fractions were measured by equilibrium dialysis using radiolabelled cortisol. Dialysis was carried out in a 'Dianorm (Diachema A.G., Rüschlikon, Switzerland) equilibrium dialyser', as described elsewhere (Vleugels 1984). The interassay coefficient of variation, determined by including a control serum in duplicate in each series of measurements, was 6·8%. The intra-assay coefficient of variation was calculated with the duplo-deviation of five samples included in 11 series of measurements and appeared to be 8·5%.

Parasitaemia. This was determined in May-Grünwald-Giemsa stained blood smears. The parasites were counted against 200 leucocytes. This number was multiplied by a factor of 30, assuming a standard leucocyte count of 6000/μl, which was obtained from a survey of the local population. The parasite densities were classified according to Bruce-Chwatt (1958). The Positive Parasite Density Index (PPDI; WHO 1963) indicates the average parasite density in a number of positive smears.

Clinical malaria. This was diagnosed when women exhibited clinical symptoms of malaria (e.g. complaint of headache, pain in the joints/limbs/back, general malaise, fever), and this was confirmed by parasitology.

Results

Parity in relation to malaria prevalence and parasite density

Clinical malaria was seen significantly more frequently in nulliparas (36%) than in multiparas (19%; Fisher's exact test: $P<0{\cdot}001$). The mean PPDI was 6·0 (SD 2·0) in nulliparas and 5·9 (SD 2·1) in multiparas; this difference was not statistically significant (Student's *t*-test: $P = 0{\cdot}76$).

Serum concentration of total cortisol related to gestation, parity and malaria

The serum concentrations of total cortisol in women with actual clinical malaria and in those without recorded clinical malaria were plotted against gestational age (Fig. 1).

Linear relations between cortisol and gestation were found ($y = 0{\cdot}49 + 0{\cdot}21\,x$ and $y = 0{\cdot}17 + 0{\cdot}022\,x$; y = cortisol concentration μmol/l; x = gestation in weeks). Assuming parallelism of regression lines (parallelism test: $P = 0{\cdot}71$), the cortisol level in the group with clinical malaria was significantly higher ($P<0{\cdot}001$) according to a one-way analysis of covariance. The difference amounted to 0·29 μmol/l).

Since parity was not considered in the previous analysis, the groups of women with and without clinical malaria were subdivided into nulliparas and multiparas and their serum concentrations of total cortisol were plotted against

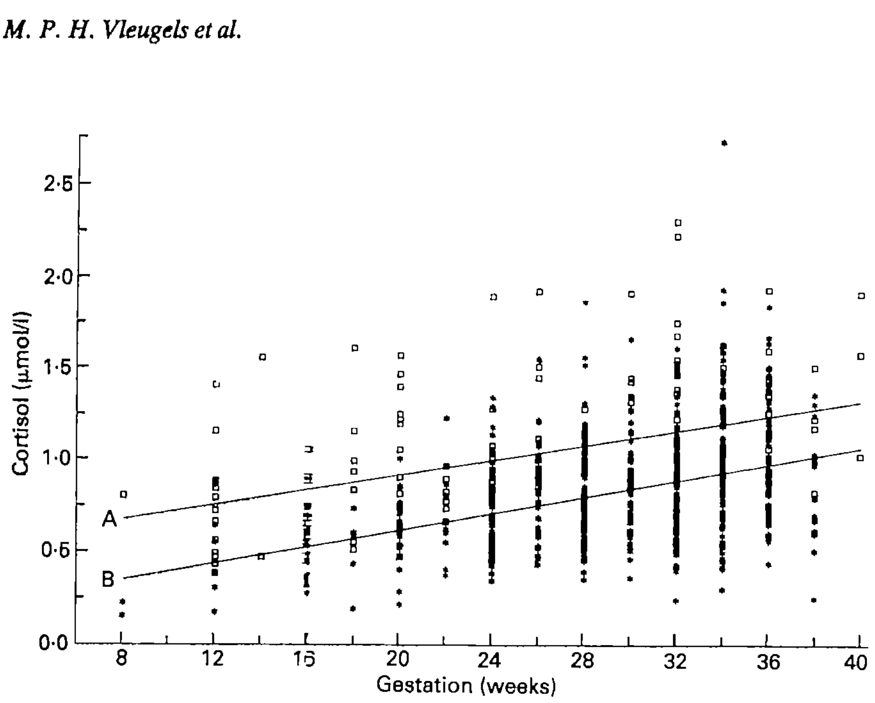

Fig. 1. Serum concentrations of total cortisol in pregnant women with (□) and without (*) clinical malaria and their corresponding regression lines (A, with malaria; B, without malaria)

gestation (Figs 2 and 3). The data were analysed by a two-way analysis of covariance with the factors clinical malaria and parity and the covariable gestational age. The mean cortisol concentration of each of the four sub-groups is given in Table 1. The interaction hypothesis of an equal difference between nulliparas and multiparas for malarious and non-malarious women

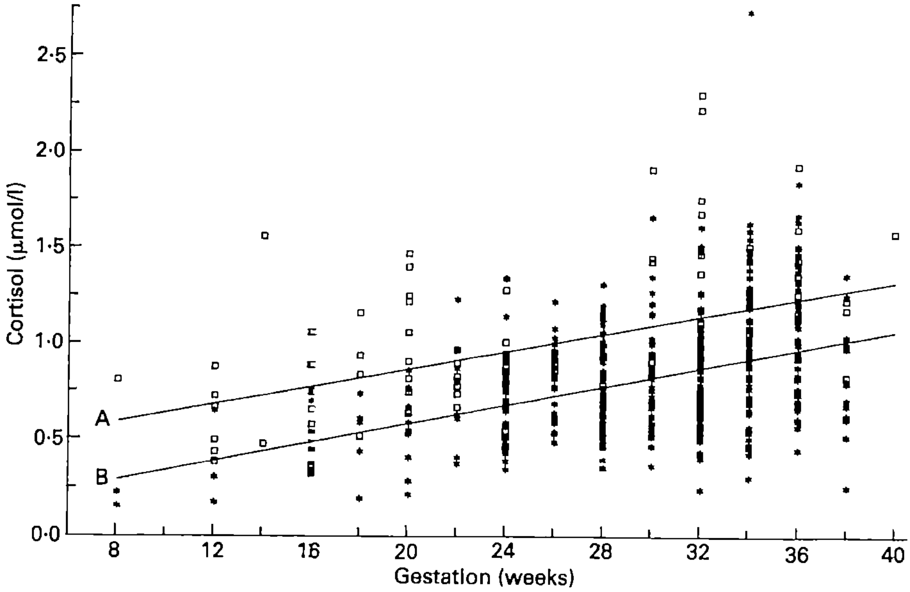

Fig. 2. Serum concentrations of total cortisol in pregnant nulliparas with (□) and without (*) clinical malaria and their corresponding regression lines (A, with malaria; B, without malaria).

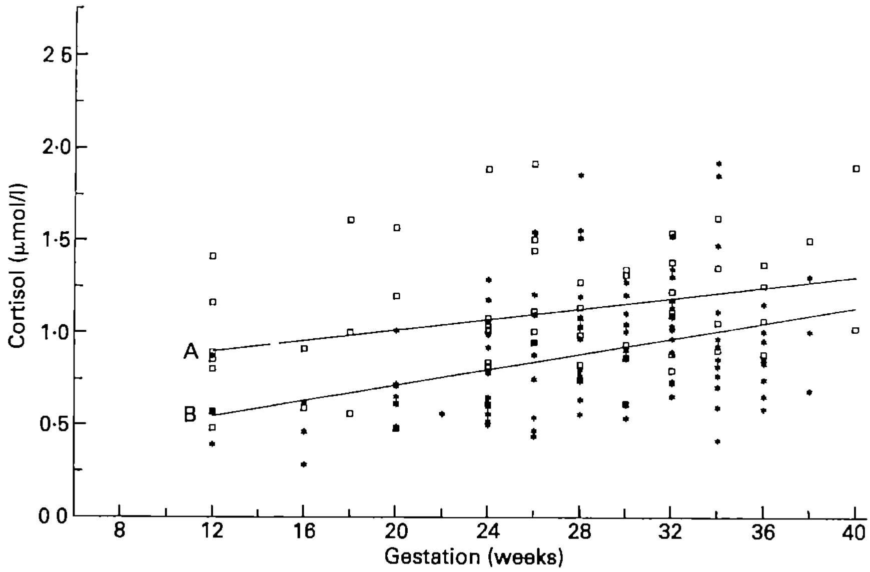

Fig. 3. Serum concentrations of total cortisol in pregnant multiparas with (□) and without (*) clinical malaria with their corresponding regression lines (A, with malaria; B, without malaria).

could not be rejected ($P = 0{\cdot}82$). Again a highly significant effect ($P<0{\cdot}001$) for the factor malaria was found. The difference between nulliparas and multiparas also appeared to be significant ($P = 0{\cdot}002$).

Total cortisol concentration and the loss of malaria immunity during pregnancy

The results described indicate a relation between the level of cortisol and clinical malaria. An important question is whether increased cortisol levels are causative of or merely associated with clinical malaria.

A causative relation was put forward in an experimental malaria study (van Zon *et al.* 1982, 1985*b*). In an attempt to analyse this in our study group, we compared the serum cortisol concentrations measured during a non-malaria visit preceding a malaria visit in malarious women with the corresponding data obtained in non-malarious women.

The data were analysed by a two-way analysis of covariance with gestational age as a covariable. The mean cortisol concentrations adjusted for difference in gestation are given in Table 2. No significant interaction between malaria and parity was found ($P = 0{\cdot}52$). Although women with a recorded clinical malaria exhibited higher mean cortisol values than those without clinical malaria, the difference is not statistically significant ($P = 0{\cdot}40$).

We also compared cortisol concentrations measured during non-malaria visits after clinical malaria in malarious women with the corresponding values in the non-malarious women. Since the non-malaria visits after clinical malaria took place between 20 and 38 weeks gestation, only the cortisol values from visits after 20 weeks gestation were considered in the non-malarious group. The mean cortisol values adjusted for differences in gestation are shown in Table 3.

Again a two-way analysis of covariance with gestation as covariable, and malaria and parity

Table 1. Adjusted mean total cortisol concentration (μmol/l) in non-malarious women and in malarious women during malaria visits, subdivided by parity

Parity	Non-malarious group	Malarious group
Nulliparas	0·89 ($n = 105$)	1·15 ($n = 57$)
Multiparas	0·79 ($n = 422$)	1·07 ($n = 95$)

The means are recalculated for 28·8 weeks gestation (the mean of all visits) on the basis of a linear relation.

Table 2. Adjusted mean total cortisol concentration (μmol/l) in non-malarious women and in malarious women during a non-malaria visit preceding a malaria visit, subdivided by parity

Parity	Non-malarious group	Malarious group
Nulliparas	0·91	0·92
	(n = 105)	(n = 10)
Multiparas	0·80	0·89
	(n = 422)	(n = 14)

The means are recalculated for 29·3 weeks gestation (the mean of all visits) on the basis of a linear relation.

as factors, was applied to the data. No significant interaction between malaria and parity was found (P = 0·27). Among the nulliparas the malarious women had a higher mean cortisol concentration after the malaria attack than was found in the non-malarious women However, no overall significant malaria effect could be established (P = 0·24). The mean time difference between the visit with clinical malaria and the subsequent non-malaria visit was 65 days. The long interval makes it unlikely that the high cortisol level found at the non-malaria visit was still caused by malaria itself.

The correctness of the assumption of a linear increase of total cortisol levels towards a recrudescence was analysed further. The averaged increase of total cortisol in malarious women during non-malaria visits both before (Table 2) and after a malaria attack (Table 3) was 0·10 μmol/l, whereas the malaria effect was about 0·29 μmol/l (see above).

These data suggest that the increase towards a malaria visit is not linear for women who develop clinical malaria. Thus, an increasing period between two sampling visits (Table 2) may reduce the rate of increase and thereby the chance to detect significant differences. More sampling points are needed to characterize the period of cortisol increase towards an attack of clinical malaria.

Free serum cortisol concentration related to malaria and parity

The fraction of free cortisol was determined in randomly chosen sera from 29 women with clinical malaria, and 28 women without recorded malaria during pregnancy. Following the results of the above analysis, it was presumed that the influence of gestation, parity and clinical malaria on the concentrations of free cortisol was proportionally not different from that observed on total cortisol.

The influence of parity and malaria on the fraction of free cortisol was analysed by a two-way analysis of variance. Since preliminary tests did not reveal a clear effect of gestation on the fraction of free cortisol this factor was not accounted for. The means of the four subgroups are given in Table 4. The interaction hypothesis of an equal difference between nulliparas and multiparas for malarious and for non-malarious women could not be rejected (P = 0·40). The free cortisol fraction tended to be higher in nulliparas than in multiparas averaged over women with and without clinical malaria (P = 0·06). No significant difference was found between malarious and non-malarious women (P = 0·54).

Discussion

This study confirms previous observations (Kortman 1972; Bruce-Chwatt 1983) that pregnant women exhibit a high incidence of malaria, particularly in the first pregnancy.

This led to the hypothesis that malaria immunity is suppressed during pregnancy particularly in primigravidae. The idea was supported by the many immunosuppressive substances that have been found in pregnancy sera (Fabris *et al.* 1976; for review see also Vleugels 1984; van Zon 1984). The possible effect of changes in the serum glucocorticoid concentration on loss of malaria immunity during pregnancy was extensively analysed in an experimental *Plasmodium berghei* mouse model (van Zon *et al.* 1982, 1985*a*,*b*). These studies provided a strong

Table 3. Adjusted mean total cortisol concentration (μmol/l) in non-malarious women and in malarious women during a non-malaria visit subsequent to a malaria visit, subdivided by parity

Parity	Non-malarious group	Malarious group
Nulliparas	0·93	1·05
	(n = 98)	(n = 16)
Multiparas	0·83	0·83
	(n = 402)	(n = 21)

The means are recalculated for 30·4 weeks gestation (the mean of all visits after 20 weeks) on the basis of a linear relation.

Table 4. Mean fractions of free cortisol in pregnant women with respect to parity and clinical malaria

	Non-malarious group	Malarious group	
Parity	Mean (SD)	Mean (SD)	Mean of means
Nulliparas	4·8 (1·0) (n = 10)	5·5 (2·9) (n = 15)	5·1
Multiparas	4·3 (0·9) (n = 18)	4·2 (1·2) (n = 14)	4·2
Mean of means	4·5	4·8	

indication for a causative relation between changes in serum corticosterone concentration and loss of malaria immunity during pregnancy. Cortisol has strong immunosuppressive properties in man (Cupps & Fauci 1982) and the level is higher in first than in later pregnancies (Vleugels *et al.* 1986). These observations justified analysis of a relation between serum cortisol concentration and malaria relapses in pregnant women.

Since malaria parasites can usually be found in the blood of a considerable proportion of the population in a holoendemic area, independent of the presence of clinical symptoms, loss of malaria immunity during pregnancy was defined in relation to clinical symptoms, and only accepted when confirmed by parasitology.

Since, inevitably, the women in the study were not under continuous surveillance and could be sampled to a limited extent only, the study groups of women with or without a recorded clinical malaria are inevitably 'contaminated'.

Nevertheless, statistical analyses revealed results that are in line with those observed in the experimental murine model. Women with clinical malaria had a significantly higher total cortisol concentration than those without clinical malaria during pregnancy. The increased total cortisol concentration found in both parity groups was independent of gestational age. Analysis of the total cortisol concentrations during a non-malaria visit both before and after an attack of malaria suggests the possibility that increased levels are already developed before the relapse and persist afterwards. The number of sampling points, particularly around the period of clinical malaria, should be increased to obtain a more definite picture. The result is in line with changes in serum corticosterone observed in relation to a relapse in pregnant mice (van Zon *et al.* 1982). Since the fraction of free cortisol is not significantly increased during clinical malaria the increased total cortisol concentration is apparently not due to a temporary stress-related secretion of cortisol.

The parallelism observed between changes in total and free cortisol does not allow indication of either of them as the causative immunosuppressant. Rosner *et al.* (1982) showed that some of the immunosuppressive effects of cortisol can be induced equally well by free or bound (to CBG = corticoid binding globulin) cortisol. As in the murine model (van Zon *et al.* 1982) the concentration of total cortisol in the plasma/serum is a suitable index.

Our observations support the suggestion that serum cortisol has a role in the regulation of malaria immunity during pregnancy, as was already more firmly established in the murine malaria model (van Zon *et al.* 1982, 1985*a*, *b*). The better immunity in multiparas with a lower frequency of malaria than in nulliparas is difficult to analyse in the human situation. Many reports indicate a pregnancy-related suppression of cell-mediated rather than humoral reactivity, which may be functional in the survival of the fetal allograft (Gusdon 1983).

An increased cortisol concentration may not only suppress cellular immune reactivity to prevent destruction of the fetal implant, but may also create the possibility for the maternal immune system to reinforce or to induce other immune reactions, e.g. humoral responses.

Altered immune reactivity may protect in a subsequent pregnancy, as suggested in the murine malaria model (van Zon *et al.* 1985*a*). Whether the differences in the cortisol level between first and later pregnancies play a role in the lower frequency of malaria relapses in multiparas remains to be determined.

Acknowledgments

The technical assistance of C. C. Hermsen, J. Peters, M. Felten and J. Mulder is gratefully acknowledged. We are also indebted to the team of the Turiani Hospital and to the team of the Laboratory of Chemical and Experimental Endocrinology (Head: Th. Benraad, MD, PhD) from the University of Nijmegen for their guidance during measurement of the serum samples. We also thank J. H. J. M. Meuwissen, MD, PhD, head of the Department of Gynaecology/Obstetrics, St Joseph Hospital Eindhoven, for his critical reading of the manuscript, and MICRO-MEDIC Systems, who provided the AUTOPAK-kits.

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Received 16 October 1986
Accepted 1 January 1987

British Journal of Obstetrics and Gynaecology
August 1987, Vol 94, pp 765–767

The effect of severe pre-eclampsia on the pancreas: changes in the serum cationic trypsinogen and pancreatic amylase

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Summary. In 13 patients with severe pre-eclampsia mean serum concentrations of cationic trypsinogen and amylase were statistically significantly higher at 64 ng/ml and 1·6 μmol/l, respectively, than the corresponding mean serum concentrations in 30 normal pregnancies, 22 ng/ml and 1·1 μmol/l respectively. These rises exceeded the expected increased values due to the slight reduction of the renal function in the pre-eclamptic patients, and therefore indicate a concomitant injury of the pancreas.

The aetiology of pre-eclampsia is unknown, but the pathophysiological disturbances consisting of vasoconstriction and oedema in various organs such as the kidneys, the brain and the liver are well known (Lindheimer & Katz 1981). It is likely that other organs can also be affected, and since no reports exist on the effect of pre-eclampsia on the pancreas, we compared pancreatic function, assessed by changes in serum levels of cationic trypsinogen and pancreatic amylase, in severely pre-eclamptic patients with that in normal pregnant women.

Patients and methods

The study included 13 pregnant women, between 18 and 36 years of age who had pre-eclampsia (blood pressure > 140/90 mmHg and proteinuria > 0·5 g/l), one was in the second trimester and 12 were in the third trimester. The comparison groups comprised 30 healthy women, between 20 and 36 years of age, there were 10 women in each of the first, second and third trimesters of normal pregnancy. All subjects gave informed consent to the study. In the pre-eclamptic group the mean arterial blood pressure at the time of investigation was 166 (SD 20)/110 (SD 12) mmHg, and the mean urinary protein excretion 5·8 (SD 6·3) g/24 h. Three patients were treated with antihypertensives before the blood sampling. One patient received atenolol, 50 mg×2 for 2 days, and two patients had methyldopa, 250 mg×3 for 4 days, and 500 mg×3 for 3 days, respectively.

Blood samples were drawn after an overnight fast. Serum pancreatic amylase was determined by the chromogenic enzyme test 'Phadebas Isoamylase Test' kindly provided by Pharmacia (Uppsala, Sweden) with an expected mean value 1·4 (95% range 0·6–3·3) μmol/l, and serum cationic trypsinogen by a radioimmunoassay method (Florholmen *et al.* 1984) with an expected mean value of 26 (95% range 11–41) ng/ml in non-pregnant women.

The significance of differences in the serum concentrations between the various groups of subjects were evaluated by a two-tailed

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Wilcoxon's unpaired rank test, and $P<0{\cdot}05$ was considered statistically significant. The coefficients of correlation between the serum concentrations of amylase and cationic trypsinogen on one hand and the creatinine clearance on the other were evaluated by Student's *t*-test, and $P<0{\cdot}05$ was considered statistically significant.

Results

Table 1 shows the serum creatinine, the creatinine clearance, the serum trypsinogen and the serum pancreatic amylase in the pre-eclamptic group, and in the three gestational age groups of normal pregnancies. Serum concentrations of creatinine, cationic trypsinogen and pancreatic amylase were all significantly higher in the pre-eclamptic group than in any of the groups of normal pregnancies.

In the pre-eclamptic group the coefficient of correlation between the creatinine clearance and the serum cationic trypsinogen was −0·45 (NS), and between the creatinine clearance and the serum pancreatic amylase −0·39 (NS).

Discussion

Our findings show that in severe pre-eclampsia serum concentrations of cationic trypsinogen and pancreatic amylase are both significantly higher than serum concentrations in normal pregnancies. In the pre-eclamptic group renal function, as indicated by serum creatinine and creatinine clearance, was slightly lower than in normal third trimester pregnancies (Øian *et al.* 1984). Studies have indicated some form of renal clearance of endogenous cationic trypsinogen (Borgstrom & Ohlsson 1978), while most of the endogenous amylase is excreted by the kidneys (Pasternick & Klockar 1978). Therefore, it is not surprising that both the serum cationic trypsinogen and the serum pancreatic amylase are increased in patients with reduced renal function. However, this reduction in the renal function was poorly and non-significantly correlated with the increase in serum levels of the pancreatic enzymes. In fact the serum cationic trypsinogen levels reached values seen in patients with acute pancreatitis (personal observation). Accordingly, it seems unlikely that the slight reduction in renal clearance of the pancreatic enzymes alone can account for the increased serum levels of cationic trypsinogen and pancreatic amylase observed in the patients with pre-eclampsia. It is also unlikely that the antihypertensive treatment in three of the patients had any effect on our measurements.

In pre-eclampsia several organs such as the kidneys, brain and liver may be affected, but we have not found any report of overt pancreatitis as a manifestation of pre-eclampsia, although pancreatitis has been suggested as a cause of abdominal pain in pre-eclampsia (Ferris 1983).

We have earlier found that pancreatitis can occur in hypovolaemic shock (Florholmen *et al.* 1985*a,b*). It would appear, therefore, that the increased serum levels of cationic trypsinogen and pancreatic amylase, found in pre-eclampsia, have to be ascribed not only to a reduction in the renal clearance of these pancreatic enzymes, but also to an increased release of pancreatic enzymes into the blood provoked by cellular damage of the pancreas. This apparent pancreatic damage may also activate various pancreatic enzyme systems together with the complement and the kinin systems (Lasson 1984). This may

Table 1. The renal and the pancreatic functions in the groups studied

Study group	*n*	Serum creatinine (μmol/l)	Creatinine clearance (ml/min)	Serum cationic trypsinogen (ng/ml)	Serum pancreatic amylase (μmol/l)
Pre-eclampsia	13	84 (14)*	97 (43)	64 (44)*	1·6 (0·8)*
Normal pregnancies					
First trimester	10	66 (7)		23 (5)	0·9 (0·4)
Second trimester	10	64 (7)		23 (10)	1·0 (0·7)
Third trimester	10	71 (7)		22 (7)	1·3 (0·7)
All normal pregnancies	30	67 (8)		22 (7)	1·1 (0·7)

Results are means (SD).
*Significantly different from all groups of normal pregnancies $P<0{\cdot}05$.

cause further deterioration of the circulation in patients with severe pre-eclampsia.

Acknowledgments

We appreciate the superb technical assistance of Ingrid Christiansen, Aase Bendiksen, Jorunn Hansen and Nina Vassvik. The Phadebas Isoamylase Test was kindly provided by Pharmacia (Oslo, Norway). The present work was supported by Norwegian Research Council for Science and the Humanities, Norsk Forening til Kreftens Bekjempelse, Norsk Råd til bekjempelse av Fordøyelsessykdommer, Nordisk Insulinfond, Helga Sembs Fond, Landsforeningen mot Kreft, and Aakres Fond.

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Received 30 June 1986
Accepted 15 December 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 768–773

Salpingoscopy: a new pre-operative diagnostic tool in tubal infertility

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Summary. Endoscopy of the fallopian tube allows examination of the tubal mucosa in subfertile patients. Clinical and morphological studies have shown a high correlation between the appearance of the tubal mucosa and the ultimate outcome in terms of pregnancies. Salpingoscopy was originally performed during laparotomy for reconstructive tubal surgery. The present study describes the use of a rigid 3 mm telescope passed along the channel of the operating laparoscope to assess the mucosa of the infundibulum and ampullary segment. Lesions of the infundibulum and ampullary segment have been detected in patients with apparently normal tubes on the hysterosalpingogram and at laparoscopy. The extent of the mucosal lesions can be assessed pre-operatively in patients with tubal adhesions, tubo-cornual or isthmic lesions and hydrosalpinges.

Recent scanning electron-microscopic studies of the fallopian tube have demonstrated that tubal infertility is frequently associated with lesions of the tubal mucosa such as flattening and loss of folds, adhesions, agglutination, pseudoglandular space formation and polyp formation (Vasquez *et al.* 1980, 1983*a*, *b*). These lesions are frequently not suspected on the hysterosalpingogram or at laparoscopy but are considered as a major cause of failure after reconstructive tubal microsurgery.

Several studies have examined the tubal mucosa at the time of surgery using the operating microscope (Boer-Meisel *et al.* 1986), tubal microbiopsies (Brosens & Vasquez 1976) and recently by endoscopy (Henry-Suchet *et al.* 1985). The perlaparoscopic examination of the tubal mucosa using a flexible bronchoscope was recently described by Cornier (1985).

In the present study we investigated the practicability of tubal endoscopy at the time of laparoscopy and its usefulness in the diagnosis of tubal lesions in patients suspected of tubal infertility.

Subjects and methods

In 44 patients endoscopic inspection of the mucosa of the ampullary tubal segment was performed at the time of diagnostic laparoscopy using a rigid 3 mm telescope passed along the channel of the operating laparoscope. The essential step before introducing the endoscope is the alignment of the fallopian tube with the axis of the laparoscope. In most cases this can be achieved by fixing the uterus with an intrauterine cannula and moving the fundus of the uterus into the fossa ovarica after lifting the adnexum. By presenting the adnexum on the anterior surface of the uterus, the fimbriae and ampulla are easily accessible for the telescope, although sometimes the tube needs to be held steady and brought

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into alignment with an atraumatic forceps introduced through a second incision. A 3 mm probe is used to identify the abdominal ostium of the tube and the telescope is introduced with its sheath connected to a saline infusion set. Using a moderately fast flow, the tube is distended and this allows the telescope to be advanced progressively, under direct vision, with the light source attached to the endoscope. In most cases the endoscope can be advanced up to 3 or 4 cm along the ampullary segment. The mucosa is inspected while the folds are floating in the lumen distended by the saline solution.

If tubo-ovarian adhesions prevent access, the fallopian tube is first mobilized by lysis of the adhesions. Hydrosalpinges are opened by a small incision at the site of the occlusion to enable the introduction of the telescope into the ampulla. Haemostasis is achieved with endothermic coagulation. Tubal endoscopy was not attempted when the hysterosalpingogram and the laparoscopic assessment of the pelvic organs indicated that operative treatment was impossible.

A group of 25 patients with proven fertility undergoing laparoscopy or surgery which was not related to infertility was used as a control group.

Results

Control group

Salpingoscopy showed the large and numerous folds of the fimbriae orientated towards the infundibulum (Fig. 1). The ampullary segment was characterized by three to five major folds with secondary folds arising from these and several minor folds interspaced between the major folds (Fig. 2). The major and minor folds were approximately 4 and 1 mm in height respectively. The thin secondary folds had a delicate vascular network.

Infertile patients

Patent tubes. In 27 patients the tubes were normal on the hysterosalpingogram. However, in seven patients abnormalities of the folds were seen at salpingoscopy such as agglutination or adhesions (Figs 3 and 4). Inflammatory reaction was identified by the prominent aspect of the vascular pattern. A segmental circular stricture of the ampullary segment was seen in one patient with a diethylstilboestrol-syndrome.

Tubocornual and isthmic lesions. Four patients had lesions of the tubocornual or isthmic segment on the hysterosalpingogram or at laparoscopy. In addition, abnormalities of the ampullary mucosa were seen in two of these patients.

With hydrosalpinges. The ampullary mucosa was inspected in 13 patients in whom uni- or bilateral hydrosalpinges were diagnosed on the hysterosalpingogram. The fallopian tube was opened (Fig. 5) and mucosal lesions were observed such as distended and flattened major folds, focal or extensive lesions such as adhesion, agglutination or complete loss of folds or stricture of the lumen (Fig. 6). In two patients salpingoscopy revealed a false radiographic diagnosis of hydrosalpinx. In one of these patients, the mucosal fold pattern at the infundibulum was normal but in the ampullary segment the major folds were very distended and the minor folds were flattened. The tubal wall appeared extremely thin and transparent suggesting structural abnormality of the myosalpinx (Figs. 7 and 8).

Failure and complications

In 7 out of 44 patients the telescope could not be introduced in one or both fallopian tubes. Intratubal bleeding did not occur. Mild bleeding occurred from the site of the incision of the hydrosalpinx or occasionally from grasping the salpinx with the atraumatic forceps, but stopped spontaneously or was easily controlled by endothermic coagulation.

Discussion

The present study proves that salpingoscopy is a useful addition to pelvic endoscopy. A rigid 3 mm telescope can be introduced into the ampullary segment for 3 to 4 cm without causing tubal damage. Adaptation of the instrumentarium is likely to improve the access up to the ampullary-isthmic junction.

Lesions of the tubal mucosa have been demonstrated in patients with normal, patent tubes as judged by the hysterosalpingogram and laparoscopy. In patients with tubocornual blocks it is the only method by which the ampullary segment can be assessed. Tubocornual anastomosis for cornual blocks has a good prognosis

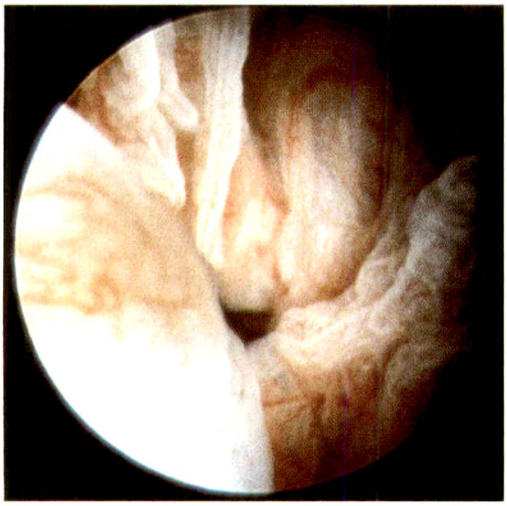

Fig. 1. The normal infundibulum is characterized by several large folds arranged radially. The blue colour is due to the transcervical injection of methylene blue.

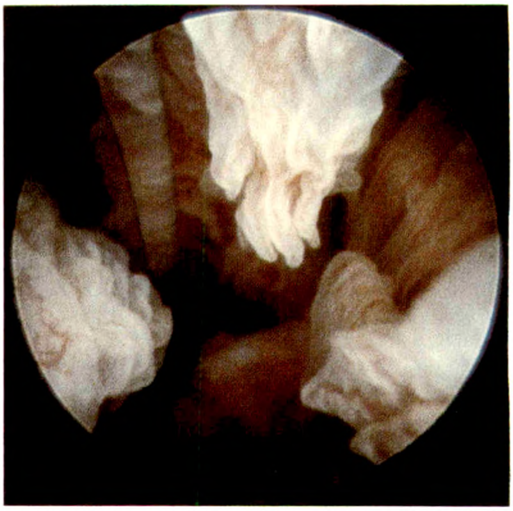

Fig. 2. The normal ampullary mucosa is composed of three to six major folds with secondary folds arising from them and several minor folds between them.

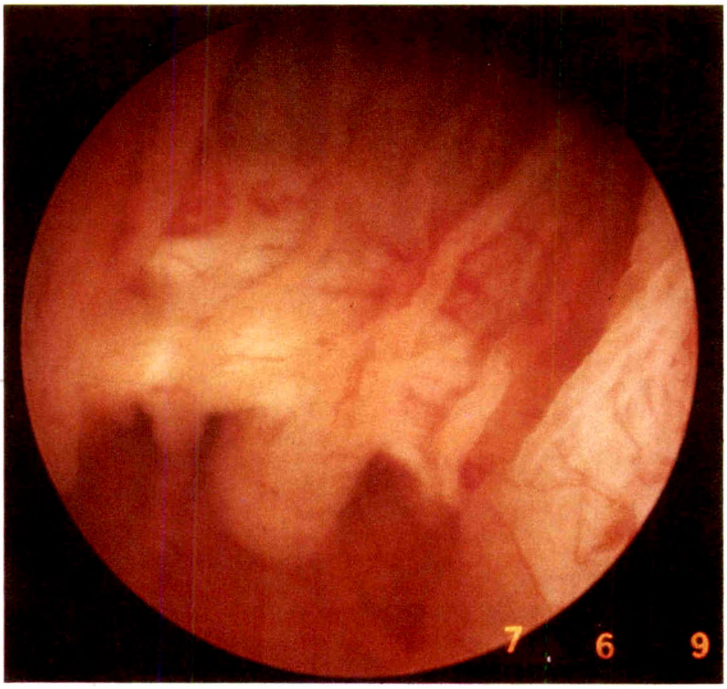

Fig. 3. The normal ampullary mucosa of the right tube in a patient presenting with infertility.

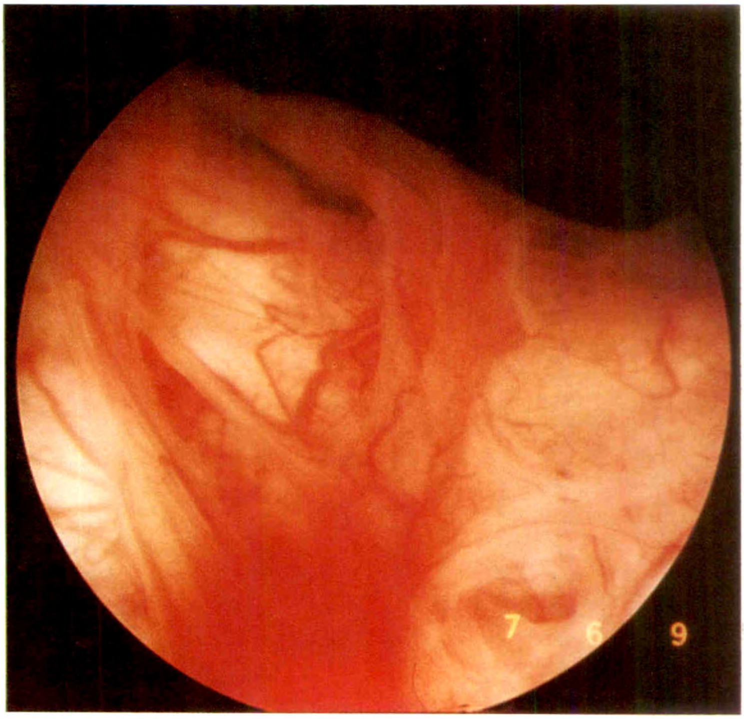

Fig. 4. The ampullary mucosa of the left tube from the same patient as in Fig. 3 shows adhesions between the folds.

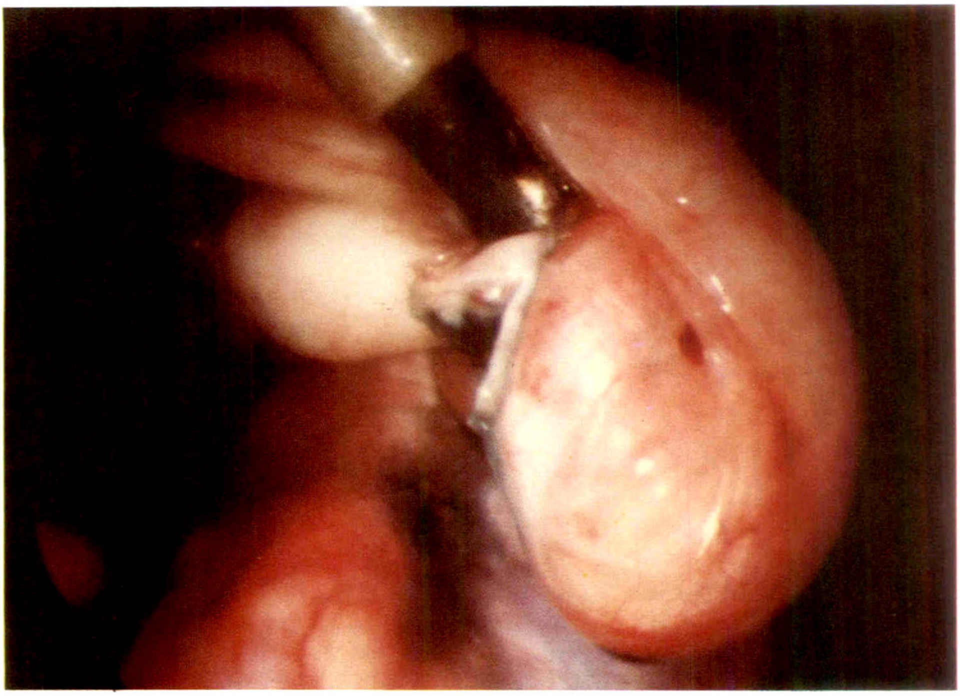

Fig. 5. A small fish-mouth opening allows the introduction of the endoscope.

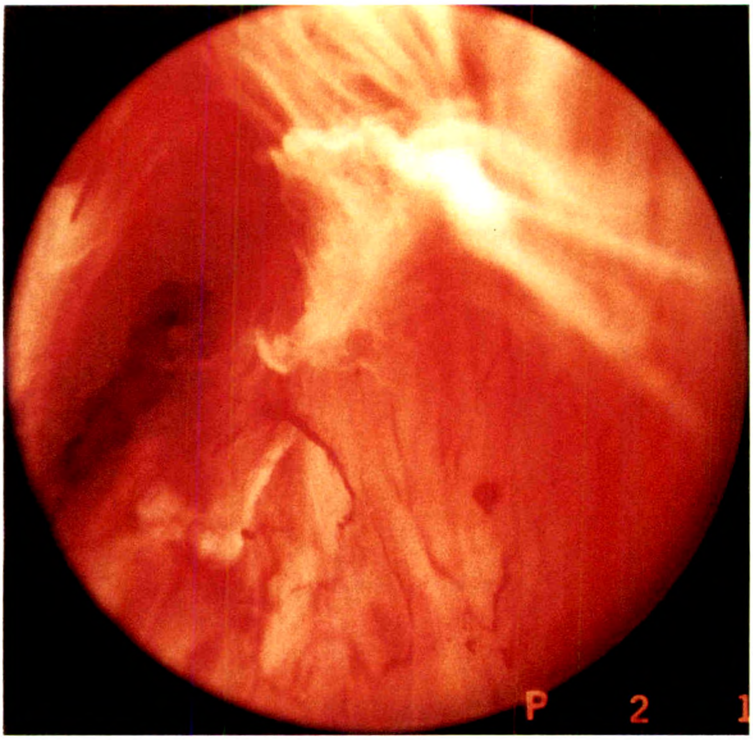

Fig. 6. Hydrosalpinx: the mucosa shows multiple adhesions of the folds.

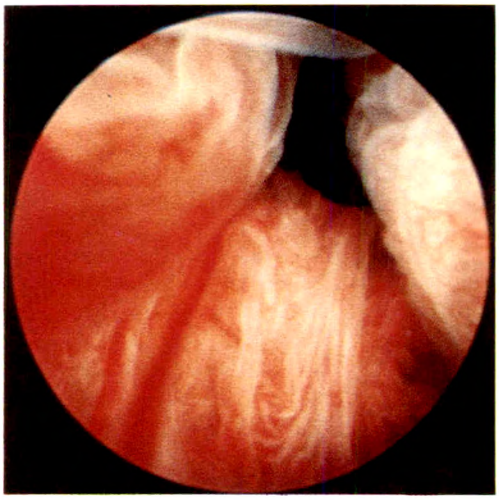

Fig. 7. The abdominal ostium of the tube in a patient with a radiological diagnosis of hydrosalpinges. The inspection of the infundibulum is normal and the tuboscope is introduced without difficulty.

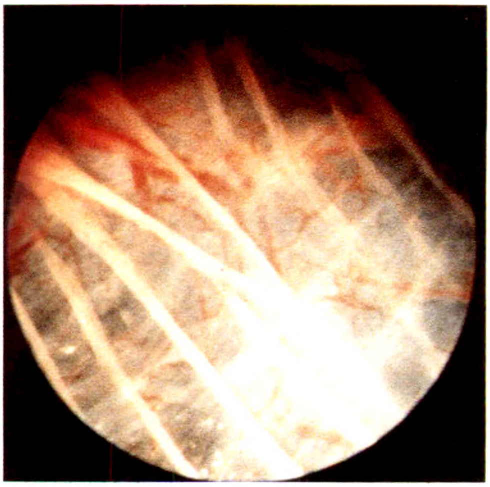

Fig. 8. In the ampullary segment from the same patient as in Fig. 7, the major folds are separated and the minor folds are flattened. The tubal wall is very thin and transparent. The findings are suggestive of structural abnormality of the mysosalpinx.

if the lesions are not bipolar, but restricted to a short segment (Winston 1981). Also in hydrosalpinges the mucosa can be examined before laparotomy is performed. Recent peroperative studies have shown that after salpingostomy a 77% pregnancy rate may be obtained in patients with thinwalled hydrosalpinges and a normal-looking mucosa (Boer-Meisel *et al.* 1986). In a recent prospective multicentre study, Vasquez, Boeckx, Brosens, Evers & Vemer (unpublished work) have demonstrated that in the absence of mucosal lesions such as agglutination or adhesions, microsurgical repair of the hydrosalpinx results in a 50% pregnancy rate. On the other hand, in the presence of mucosal folds with multiple adhesions forming bridges or pseudoglandular spaces and a thickened wall the prognosis for pregnancy is very poor.

Preliminary experience with salpingoscopy indicates that the technique is a useful tool in the diagnosis of tubal lesions which are not identified by hysterosalpingography or laparoscopy and in the investigation of the extent of tubal lesions in patients with tubo-ovarian adhesions, tubocornual or isthmic lesions or hydrosalpinges. The technique will help to refine the indication for tubal microsurgery and the selection of patients for gamete intra-fallopian transfer or in-vitro fertilization. Prospective studies are now in progress to determine the prognostic value of tuboscopy in terms of risk for ectopic pregnancy.

Acknowledgments

We should like to thank Mr Hiltebrandt from Richard Wolf Endoscopes for developing the prototype salpingoscope and Mr Fransen from Carl Storz for providing endoscopic material.

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Received 25 June 1986
Accepted 21 September 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 774–778

The value of artificial insemination with husband's semen in infertility due to failure of postcoital sperm-mucus penetration—controlled trial of treatment

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Summary. Artificial insemination with husband's semen into the cervical canal and uterine cavity (high AIH) was assessed by a randomized controlled prospective study in 46 couples whose infertility was due to failure of sperm mucus penetration, as defined by negative postcoital tests, after excluding all interfering female factors and men with sperm density $<1 \times 10^6$/ml. Seminal analysis was abnormal in 18 of the 46 men and sperm antibodies in semen were detected in 19 of the remaining 28 with normal seminal analysis. Overall, the cumulative conception rate after 6 months with AIH was 4·7 (SE 3·8)% and without treatment was 6·6 (SE 3·9)%. The results were unaffected by the findings on seminal analysis or by the presence or absence of sperm antibodies in semen. AIH appeared to be of no benefit.

Artificial insemination with husband's semen is the most widely used treatment for male infertility, usually presumed because of oligospermia, and for what is called 'mucus hostility' when there is failure of sperm penetration of cervical mucus despite normal seminal analysis. There is growing interest in the use of specially prepared sperm injected directly into the upper uterine cavity, but at present the most common practice is simply to use whole fresh semen injected into the upper cervical canal and thus indirectly into the uterus, so called high AIH. This paper concerns the latter method. Because of the known possibility of conception without treatment (Nachtigall *et al.* 1979), properly controlled study is essential. The aim of this controlled prospective study was to determine the true benefit of AIH, carefully excluding interfering female factors and comparing time-specific cumulative conception rates.

One underlying problem in assessing treatment is unreliability in the diagnosis. Standard seminal analysis is a relatively poor predictor of male fertility (Glazener 1984; Glazener *et al.* 1985). Men with normal seminal analysis are often proved infertile, when sperm function is assessed by determining post-capacitation movement characteristics and penetration of hamster eggs *in vitro* (Aitken *et al.* 1982), methods which provide much better prediction of natural conception than standard seminal analysis (Aitken *et al.* 1984). However, assessment of postcoital sperm-mucus penetration by the PCT which can be done in the clinic seems to provide equally good discrimination provided strict criteria are applied including fully developed cervical mucus (Hull *et al.* 1982*a*; Glazener 1984; Glazener *et al.* 1985). Sperm-mucus penetration correlates with fertilizing capacity *in vitro* of both hamster

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(Schats *et al.* 1984) and human oocytes (Hull *et al.* 1984; Wardle *et al.* 1985), indicating that the inherent defect is usually in the sperm rather than the mucus. Thus the idea of 'mucus hostility' is usually misplaced, a properly conducted negative PCT usually indicating male rather than female infertility (unpublished observations). Fertility is not impaired with oligospermia if the PCT is positive, but is greatly reduced even with normal seminal analysis if the PCT is negative (Glazener 1984; Glazener *et al.* 1985). We have therefore used a negative PCT, given good mucus, as the primary indication for a diagnosis of male infertility and treatment by AIH in this study, but have analysed the results also according to the seminal findings including assessment of sperm antibodies.

Methods

The study was approved by the ethics committee of the Bristol and Weston District Health Authority and patients gave informed consent. Couples with at least 1 year's infertility attending the Bristol Fertility Clinic were recruited to a 1-year study of treatment by AIH in alternate cycles, with the following diagnostic provisions. The women had normal ovarian function (cycles 21–42 days, and mid-luteal serum progesterone levels $\geqslant$30 nmol/l (Hull *et al.* 1982*b*)); normal basal serum FSH, prolactin and thyroid hormone levels; normal findings on laparoscopy which was performed if they failed to conceive within 6–12 months; and a coital frequency of at least twice weekly.

All had failure of postcoital sperm-mucus penetration as defined by a negative PCT (absence of forward-progressing spermatozoa in fully developed pre-ovulatory endocervical mucus 6–18 h after coitus) in two separate menstrual cycles (Hull *et al.* 1982*a*). The male partner was classified as having normal or abnormal seminal analysis by motile normal sperm density (MNSD) above or below 4×10^6/ml (mean of 2–3 samples) (Glazener 1984; Glazener *et al.* 1985), but men with complete or virtual azoospermia (sperm density $<1 \times 10^6$/ml) were excluded.

The presence of sperm antibodies in seminal plasma was determined by one or more of the following methods: the mixed agglutination reaction (MAR) (Coombs *et al.* 1956; Jager *et al.* 1978); the tray agglutination test (TAT) (Friberg 1974), critical titre 1/32; and the pattern of sperm-mucus penetration *in vitro* at the interface by a modified Kurzrock–Miller slide test (Miller & Kurzrock 1932; Joyce & Vassilopoulos 1981), which we have found to correlate closely with the preceding tests (Glazener 1984).

AIH was performed on alternate days during the pre-ovulatory phase of cervical mucus secretion, usually twice each cycle. A 1 ml sample of liquified semen, within 1–2 h of collection, was injected into the cervical canal from a 1 ml disposable insulin syringe with the nozzle inserted up to its shoulder to form a seal. The aim was to achieve intrauterine insemination, which was assumed from the occurrence of mild uterine cramps. Treatment was offered for six cycles alternating with six untreated cycles, commencing with or without treatment by allocation based on date of birth. Thus each woman acted as her own control. It was not possible to conduct the study double-or even single-blind.

Treated and untreated cycles were considered separately in each couple for comparison as distinct consecutive series. Cumulative conception rates were calculated as for life-table analysis (Tietze 1968), which allows for couples who did not continue as long as others in the study, and the average conception rate compared by the *t*-test.

Results

Forty-six couples were studied who met the original selection criteria and the following secondary restriction from 81 couples who were eligible for study. There was a relatively high drop out rate and in some others it proved impossible to ensure strict alternation of cycles with and without AIH. We therefore only included couples who completed six cycles with one form of treatment and at least three cycles with the other, unless they conceived earlier. Those who failed to conceive completed an average of 11·2 cycles with and without AIH. Of those who conceived, the biggest discrepancy between the number of cycles with and without AIH in any one couple was two.

The median age of the women was 28·5 years (range 19–37 years) and 28% were parous. The median age of the men was 31 years (range 18–42 years). The median duration of infertility was 29·5 months (range 12–146 months). There were no significant differences related to seminal findings or presence or absence of sperm antibodies.

Of the 46 couples studied, five conceived within the 1-year period of the study (11%) during a total of 475 cycles (1% of cycles), two in 223 cycles with AIH and three in 252 without

Table 1. Results comparing treatment with and without high AIH in couples with failure of postcoital sperm-mucus penetration, related to motile normal sperm density (MNSD) and presence of sperm antibodies in semen

Diagnostic group	Treatment	Patients (*n*)	Cycles (*n*)	Pregnancies (*n*)	Conception rate at 6 months (%) mean (SE)*
Total	Untreated	46	252	3	6·6 (3·9)
	AIH	43	223	2	4·7 (3·8)
MNSD					
<4 × 10⁶/ml	Untreated	18	100	1	5·6 (5·7)
	AIH	17	87	1	5·9 (6·8)
≥4 × 10⁶/ml	Untreated	28	164	2	7·3 (5·2)
	AIH	26	136	1	3·8 (4·5)
Sperm antibodies in semen					
Present	Untreated	19	114	0	—
	AIH	19	105	0	—
Absent	Untreated	27	138	3	11·4 (6·8)
	AIH	24	118	2	8·3 (7·1)

* Cumulative conception rates calculated by life-table method.

treatment. Only 43 couples received AIH treatment because the other three conceived without treatment (in the first or second cycle) before AIH could be given. All 46 couples entered the arm of the study without treatment because none conceived earlier with AIH. The two conceptions with AIH occurred in the first and third cycle (after one and four cycles respectively without treatment). Table 1 gives the results of treatment with and without AIH and related to the seminal findings. There were no significant differences between any of the groups.

Discussion

The results of this study show that high AIH done in the usual way is of no benefit in the treatment of male infertility, whether due to evident seminal defects or sperm antibodies in seminal plasma.

The same also applies to men with normal seminal analysis whose defective sperm function is only demonstrated by failure to penetrate good cervical mucus. Penetration of mucus is primarily an index of sperm function, being correlated with both in-vivo and in-vitro fertilizing ability. We therefore used failure of sperm-mucus penetration as the primary criterion of male infertility in all cases in our study.

Neither sperm counts, as assessed by standard seminal analysis, nor the presence of sperm antibodies in semen, made any difference to the outcome. The chance of conception was very poor, amounting to only about 6% after 6 months either with or without treatment, and about 11% overall after 12 months' exposure to both treatments.

Reported results of AIH in the treatment of oligozoospermia, poor postcoital tests, and poor sperm motility have been thoroughly reviewed by Nachtigall *et al.* (1979). There has also been a more recent and optimistic, but small and uncontrolled, study reported by Glezerman *et al.* (1984). Nachtigall *et al.* (1979) reported a mean pregnancy rate with AIH of 18%, and a range of 0–55% in individual studies. That compares with a 20% rate in untreated male infertility reported by Glass & Ericsson (1979). Nachtigall *et al.* (1979) also reported a 14% pregnancy rate after discontinuing AIH. The true value of AIH can therefore only be assessed by properly controlled prospective methods, as in the present study.

AIH for sperm antibodies in men has been reported to lead on average to a 20% conception rate (see review by Joyce & Vassilopoulos 1981). However, this finding was not related to time and, particularly important, was concerned only with antibodies in circulation, which are of questionable significance. There has been only one very small and inconclusive study dealing with antibodies in semen (Hansen & Hjort 1980). As an alternative to AIH, the use of glucocorticoid therapy for sperm antibodies has had favourable reports (Hendry *et al.* 1981; Hargreave & Elton 1982; Shulman & Shulman 1982), but needs to be assessed by controlled trial, which we are now pursuing.

We employed the method of AIH that is most widely used, but modifications might need to be considered. Glezerman *et al.* (1984) have drawn attention to the possible need for frequent inseminations because of the rapid dispersal of sperms when injected past the cervix. They undertook daily AIH up to seven times each cycle. They also employed only the first fraction of the ejaculate, both because of the greater sperm density, and because of the reduced prostaglandin content to avoid uterine cramps. Our patients were seldom troubled by severe cramps, and we have not found that these can be avoided by use of the first semen fraction. Glezerman *et al.* (1984) also used prophylactic antibiotic therapy because of a presumed risk of infection from intrauterine injection of untreated fresh semen, but we observed no sign of infection in our much larger study without antibiotics. Our own view is that the method is only likely to be improved by the use of ultrasound and/or hormonal monitoring to time inseminations more accurately to ovulation, but this remains to be demonstrated.

Another modification, in which there is now growing interest, is the intrauterine injection of sperms prepared as for in-vitro fertilization (IVF). There have been encouraging results from initial experience reported by Kerin *et al.* (1984) using sperms recovered by their own motion into suitable culture medium. However, the technique is relatively complex and its benefit needs further assessment. Hewitt *et al.* (1985) reported higher pregnancy rates with IVF than with AIH using this technique. There is also a fundamental question concerning the type of problem being treated by Kerin *et al.* (1984), which we believe was not really male infertility. Although they referred to treating men 'with poor quality semen', their patients appeared to have only mild oligospermia, and sperm-mucus penetration *in vitro* was normal. By our definition we would not consider these men subfertile, which exemplifies the difficulty discussed above of assessing treatment for apparent male infertility. We would suggest that Kerin *et al.* (1984) were really dealing with unexplained infertility. Indeed, their use of high intrauterine injection of prepared sperm would be appropriate to the theory that prolonged unexplained infertilty is commonly due to a female factor interfering with the transport of sperms in the genital tract above the cervix, as suggested by our own studies using donor insemination (Foss & Hull 1986) and in-vitro fertilization (Hull *et al.* 1984; Wardle *et al.* 1985).

Apart from male and possibly unexplained infertility, other conditions can be considered for treatment by AIH. First, there is primary failure of mucus production. Glezerman *et al.* (1984) reported pregnancies in 6 of 14 women with this problem although there were no controls. We have found this disorder occurs too infrequently for significant study, being represented in only 7% of couples with any type of sperm-mucus penetration failure. Of five patients with a primary mucus defect as the sole cause of their infertility, two conceived in 60 cycles (3%) but without treatment; there were 17 unsuccessful cycles with AIH. Our rate without treatment is comparable with that of Hewitt *et al.* (1985), who recently reported a 3% per cycle pregnancy rate with AIH using intrauterine insemination of sperm prepared as for IVF. In contrast, they achieved a 38% per cycle rate with IVF ($P<0{\cdot}01$), suggesting again that hostility against sperm may extend to the uterus and fallopian tube.

We have not used AIH for oligospermia when the PCT is positive. However, it would seem unlikely to be of benefit as the natural conception rates are as good as with normal semen, given a positive PCT (Glazener 1984; Glazener *et al.* 1985).

The remaining indication for AIH is coital failure. Treatment of the underlying psychological disorder would of course be preferable but, failing that, simple intravaginal insemination would be suitable, and might be better done by the couple themselves.

We conclude that standard intrauterine AIH for male infertility should be avoided, not only because the treatment is ineffective but also because of the psychosexual disruption it imposes on couples. More sophisticated methods await proper assessment. Our interpretation of the results with sperm prepared in culture medium as reported by Kerin *et al.* (1984) is that, paradoxically it seems, intrauterine AIH may be better applied in unexplained infertility.

Acknowledgments

We are grateful to the South Western Regional Health Authority Medical Research Committee for financial support for Dr Glazener; to Mr Crane, Department of Haematology, Southmead Hospital, for sperm antibody assays; and to Mr A. O. Hughes, Senior Lecturer in Medical Statistics, University of Bristol Department of Epidemiology and Community Medicine, for statistical advice. The information contained in this paper is from a thesis by Dr Glazener for a

Doctorate of Medicine of the University of Bristol.

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Received 19 June 1986
Accepted 5 December 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 779–783

Endocrine effects of ovarian electrocautery in patients with polycystic ovarian disease

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Summary. The mechanism by which ovarian electrocautery induces regular ovulatory cycles was studied in 16 women with polycystic ovarian disease (PCO) and compared with 25 normal fertile women who were undergoing sterilization by tubal electrocautery. Gonadotrophins (LH and FSH), prolactin, androgens, oestrogens, 17-hydroxyprogesterone and progesterone were determined immediately before operation and 24 h later. Following the sampling of blood for these tests, 100 μg of gonadotrophin releasing hormone (GnRH) was given intravenously and the LH and FSH responses were measured at 30 min. In the PCO-group, these tests were repeated after the first induced ovulatory cycle. After operation, LH increased only in the patients with PCO and this increase was associated with an enhanced response to GnRH, FSH showed a similar response to GnRH, also confined to the PCO-group. These pituitary responses are best explained by a change in ovarian feedback induced by the direct electrocautery of the glands in the PCO-group. There was little change in serum oestrogen. Prolactin showed an increment in all cases and serum androgens were reduced in all groups, most pronounced in the PCO patients, possibly as a result of the stress of operation. An ovarian factor—released or reduced by the electrocautery—seems to be responsible for the changes.

The efficiency of wedge resection of the ovaries in women with polycystic ovarian disease (PCO) to achieve ovulation and pregnancy has been known for many years, even if the operative mechanism is not well understood. Judd *et al.* (1976) reported that the main effect of wedge resection was reduced secretion of androgens, and to a lesser degree oestrogens. They were unable to demonstrate significant changes in the serum levels of the luteinizing hormone (LH) or the follicle stimulating hormone (FSH). The extreme complexity of the intra-ovarian interrelations that may be affected by wedge resection is well described by Erickson *et al.* (1985).

Gjønnæss (1984) introduced laparoscopic ovarian electrocautery as a treatment for infertility associated with PCO, and reported subsequent ovulation rates of 92% and pregnancy rates of 70%. The endocrine sequelae of ovarian electrocautery in PCO were increased LH and decreased androgen levels on the day after electrocautery (Aakvaag & Gjønnæss 1985). The results included endocrine and clinical observations weekly during the first postoperative month, and then monthly for a year. However, the results were not compared with the reaction to similar surgical procedures in normal, fertile women.

The present report extends the study of endocrine effects of ovarian electrocautery in patients with PCO, including a standardized stimulation test with gonadotrophin releasing hormone

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Table 1. Serum gonadotrophin levels and incremental response to GnRH determined before and the day after ovarian electrocautery in women with polcystic ovarian disease (PCO), or sterilization in the control series

		Serum LH (i.u./l)		Serum FSH (i.u./l)	
Patient group	*n*	Before operation	After operation	Before operation	After operation
PCO	16	14·4 (5·9) **Δ 34 6 (18 7)**	18·4 (10·1)* **Δ 48·9 (28·0)*****	5·6 (1·6) **Δ 2·4 (1·1)**	5·9 (1·6) **Δ 3·5 (1 9)***
Control series					
Luteal phase	10	5·3 (2·3) **Δ 33·2 (9·0)**	5·1 (3·1) **Δ 36·0 (10 5)**	3·8 (1·0) **Δ 2·7 (1·5)**	4·3 (1·3) **Δ 2·8 (1·8)**
Early follicular	8	7 9 (3·3) **Δ 17·5 (6·5)**	7·8 (2 7) **Δ 20·1 (13·7)**	5·9 (1·9) **Δ 2·5 (1·8)**	6·4 (2·4) **Δ 3·0 (1·5)**
Late follicular	7	10·5 (4·3) **Δ 28·7 (16 0)**	10 2 (5·1) **Δ 25·2 (15·5)**	7·9 (4·0) **Δ 3·6 (1·6)**	8·8 (3·5) **Δ 2·8 (0·8)**

LH, Luteinizing hormone; FSH, follicle stimulating hormone.

Results are means (SD), the values in bold type show the incremental response at 30 min after an intravenous injection of 100 μg GnRH.

Significance of Student's *t*-test paired comparison between pre-operative and postoperative values * $P<0·05$, $^{***}P<0·001$.

(GnRH) before and after the operation (Nillius & Wide 1972). For comparison, the hormonal responses to tubal sterilization were recorded in a control group of fertile women at different stages of the menstrual cycle.

Subjects and methods

The study included 16 infertile women with PCO. Criteria for inclusion were: (i) menstrual irregularity; (ii) an endocrine profile showing progesterone values with no luteal phase, serum LH and androgenic hormone concentrations in the upper 'physiological range' or increased, low sex hormone binding globulin (SHBG); (iii) the characteristic appearance of the ovaries with a smooth, white thickened capsule, often with small cysts.

The patients were treated by ovarian electrocautery. Through an ordinary angled Wolf laparoscope a biopsy or sterilization forceps was held against the ovarian surface, and a number of points (10–14 per ovary) were cauterized with unipolar current (1·75 MHz, 2–300 W) (Gjønnæss 1984). All the women achieved regular ovulatory menstrual cycles.

The control series consisted of 25 women who were studied during a routinely performed tubal sterilization. This group was chosen because the sterilization procedure utilized at Aker Hospital was very similar to the ovarian electrocautery in terms of premedication, anaesthesia, the laparoscopy, the unipolar current, and the forceps used on fallopian tubes were similar to those used on the ovaries in the PCO-group. Furthermore, the women in the control series had proven their fertility, and had regular menstrual periods. The control series was subdivided according to the ovulatory phase at the time of operation: luteal phase (10 cases), early follicular phase (8 cases), and late follicular phase (7 cases). The mean age in the luteal-phase group was 35·7 years (range 27–46), and in the follicular-phase group it was 37 years (range 28–43), somewhat higher than that in the PCO-group (28·6 years, range 24–33).

Blood samples were obtained before laparoscopy, and on the morning after (21–24 h after the laparoscopy). In the PCO-group blood samples were again obtained on the 10th day after the start of the first induced menstrual bleeding, usually 5–6 weeks after laparoscopy. GnRH was given as a stimulation test with intravenous injection of 100 μg (Lutrefact-Hoechst). Blood for determination of LH and FSH was taken before and 30 min after the injection. The recorded response was the difference between the value at 30 min and that before injection.

Hormone assays

These were performed by the routine methods in our laboratory as described previously (Aakvaag & Gjønnæss 1985).

Normal serum ranges in our laboratory were as follows: LH, 1–12 i.u./l; FSH, 1–12 i.u./l; prolactin, 50–450 m-i u./l; testosterone, 0·3–2.8

Table 2. Concentrations of steroid hormones (nmol/l), prolactin (i.u./l) and sex hormone binding globulin (SHBG) (nmol/l) determined before (B) and the day after (A) ovarian electrocautery in women with polycystic ovarian disease (PCO), or sterilization in the control series

					Control series					
		PCO			Follicular phase			Luteal phase		
Hormone		Mean	(SD)	Percentage change	Mean	(SD)	Percentage change	Mean	(SD)	Percentage change
Testosterone	B	3·11	(1·07)		1·7	(0·78)		0·94	(0·21)	
	A	2·07***	(0·95)	66	1·19**	(0·54)	70	0·87	(0·14)	93
Androstendione	B	9·37	(2·99)		5·73	(1·89)		3·61	(1·12)	
	A	5·04**	(2·63)	54	3·62*	(1·82)	63	3·11	(0·66)	86
DHT	B	1·08	(0·39)		0·70	(0·33)		0·61	(0·26)	
	A	0·67**	(0·27)	62	0·55*	(0·27)	79	0 51	(0·24)	83
DHA-S	B	7·23	(4·63)		3·97	(2·49)		3·49	(0·68)	
	A	5·43**	(3·28)	75	3·60	(2·62)	91	3·00**	(0·73)	86
SHBG	B	30·10	(13·56)		51·30	(41·40)		65·90	(25·71)	
	A	30·60	(13·37)		55·90	(43·50)		71·00	(27·30)	
Oestrone	B	0·43	(0·23)		0·40	(0·10)		0·42	(0·18)	
	A	0·35	(0·15)		0·31	(0·14)		0·44	(0·18)	
Oestradiol	B	0·23	(0·09)		0·32	(0·21)		0·47	(0·22)	
	A	0·25	(0·12)		0·26	(0·13)		0·41	(0·16)	
Progesterone	B	2·76	(1·97)		2·95	(1·55)		34·18	(11·92)	
	A	2·16	(1·26)		3·25	(2·07)		25·85	(11·15)	
17-hydroxy-progesterone	B	2·91	(0·99)		2·16	(1·34)		4·16	(1·07)	
	A	2·02	(1·26)		1·95	(1·28)		3·11	(1·07)	
Prolactin	B	267	(123)		233	(92)		285	(146)	
	A	416	(162)		315	(162)		455	(260)	

DHT, Dihydrotestosterone; DHA-S, dehydroepiandrosterone sulphate

Significance of Student's *t*-test paired comparison between preoperative (B) and postoperative (A) values *$P<0{\cdot}05$, **$P<0{\cdot}01$, ***$P<0{\cdot}001$.

nmol/l; androstenedione, 3–6·6 nmol/l; dihydrotestosterone (DHT), 0·35–1 nmol/l; dehydroepiandrosterone sulphate (DHA-S), 2–8·3 µmol/l; oestradiol (E_2), 0·4–2·0 nmol/l; oestrone (E_1), 0·1–0·7 nmol/l; progesterone: follicular-phase, 2–5 nmol/l, luteal phase, 10–60 nmol/l; 17-hydroxyprogesterone: follicular phase, 1–3 nmol/1, luteal phase, 2–6 nmol/l; SHBG 40–90 nmol/l.

Statistical significance was tested using a two-tailed Student's *t*-test. Whenever applicable, paired comparison was used.

Results

The mean serum LH level (Table 1) in the PCO-group was higher than the levels found in the control series both in the follicular-phase ($P<0{\cdot}01$) and in the luteal-phase groups ($P<0{\cdot}001$). After the ovarian electrocautery, LH levels in the PCO-group were increased at 24 h while the control series showed no such change.

The mean serum FSH level (Table 1) was very similar in the PCO and the early follicular-phase control groups, both being higher than the level in the luteal-phase groups ($P<0{\cdot}01$). After electrocautery of the ovaries and the sterilization procedure the mean FSH level increased by 10% in all groups. This increase was not statistically significant.

By the 10th day after the start of the first menstrual bleeding following ovarian electrocautery, the mean LH level had become normal in the PCO-group (6·4, SD 3·2 i.u./l) and the FSH level was unchanged (mean 5·0, SD 1·5 i.u./l).

The LH increment in response to GnRH (Table 1) was high before operation in the PCO-group, but not different from that in the luteal-phase control group ($t=0{\cdot}2328$). The follicular-phase control series, however, had a clearly poorer response to GnRH ($P<0{\cdot}05$), notably in the early follicular phase.

Ovarian electrocautery increased the LH response to GnRH by 40% ($P<0{\cdot}001$), while the sterilization procedure had no corresponding effect. During the follicular phase following the first menstrual bleeding after ovarian electrocautery, the LH response to GnRH was normalized and very similar to the value of the early follicular-phase control series (mean increment 14·0 SD 6·4 i.u./l). Table 1 also illustrates the various LH responses to GnRH during the normal ovulatory cycle, the difference between early and late follicular phase being statistically significant ($P<0{\cdot}05$). These data are in conformity with earlier publications (Nillius & Wide 1972; Heineman *et al.* 1984).

The FSH response (Table 1) to GnRH was very similar in all the groups, and only the patients with PCO showed an increase after electrocautery ($P<0{\cdot}05$). After the first induced menstrual bleeding in the PCO-group, also the FSH response was decreased (mean increment 1·9 SD 0·9 i.u./l), the difference from the pretreatment value was not significant.

The serum concentrations of the androgenic hormones were significantly higher in the PCO-group than in the control series (Table 2). The day after the ovarian electrocautery the androgens had decreased markedly in the patients with PCO. Similar reductions were seen in the control series after the sterilization procedure, but they were less marked and did not always reach statistical significance. For practical reasons the androgens were not followed later on as closely as the gonadotrophins in the PCO-group, and not at all in the control series. In some women in the PCO-group, testosterone and androstendione values were still low after the first menstrual bleeding, whereas serum DHT and DHEAS had regained the pre-cautery values. The concentration of SHBG was not influenced immediately by ovarian electrocautery.

Serum E_1 concentrations were similar in the PCO and the control groups (Table 2) but mean serum E_2 levels were lower in the PCO-group than in the control group. Electrocautery induced no significant change in the serum concentrations of E_1 or E_2, but progesterone levels decreased significantly in the luteal-phase control group. The concentration of 17-hydroxyprogesterone was related to that of progesterone with high levels during the luteal phase which decreased after the operation. Also in the PCO-group serum 17-hydroxyprogesterone concentration decreased after electrocautery ($P<0{\cdot}05$).

The changes in serum prolactin induced by electrocautery were similar in all the groups with mean increases between 30 and 60%. None of the patients had significantly elevated prolactin levels before operation.

Discussion

It is difficult to interpret these results because of the complexity in intra-ovarian steroid synthesis and regulation and the associated feedback systems of the hypothalamus and pituitary. In women with PCO, LH was significantly increased after operation, and remained unchanged in the others. The further evidence from GnRH stimulation postoperatively (Table 1), with significantly enhanced responses after operation both for FSH and LH in the PCO-group, is definitely against a down-regulation of the pituitary. These results distinctly point to a reduced negative feedback or increased positive feedback from the ovary induced by the direct electrocautery of the gland as an explanation for the observed changes in the gonadotrophins in the PCO group. Inhibiting peptides with a primary effect on FSH have been demonstrated in ovarian follicles (Channing *et al.* 1982; Grady *et al.* 1982). It is conceivable that the ovarian electrocautery, even if it is applied to the surface of the ovary, might elicit functional changes in deeper structures.

Both androgens and oestrogens have receptors on the gonadotrophs of the pituitary and on the neurosecretory cells of the hypothalamus (Næss & Attramadal 1974; Næss *et al.* 1975; Drouin & Labrie 1976). From Table 2 it is apparent that the reduction in androgens was of a considerable magnitude. The pre-operative level of androgens was highest in the patients with PCO, but some androgen reduction was present also in the women subjected to tubal electrocautery. A reduction in negative feedback due to the fall in androgens might possibly explain the postoperative LH increase, or part of it, in the patients with PCO, but it is noteworthy that there was no similar LH increase in the controls in the follicular phase that also had a significant reduction in testosterone.

The androgen reduction postoperatively occurred in all groups, admittedly not always to a degree that was statistically significant. The total impression of Table 2 is one of a generalized response in this respect. The stress of operation might be the common feature in all the women who gave this response (Funder 1984; Munck *et al.* 1984). Prolactin also increases in response to stress (Pfeiffer & Herz 1984; Adashi *et al.* 1980), and this hormone had a uniform concentration increment in all groups.

In normal physiology, E_2 is the central feedback hormone to LH in women (Knobil 1980). There is evidence for an impaired metabolic transformation of androgens to oestrogen in the polycystic ovary. As a group, our patients with PCO had low E_2 levels, and this did not change after electrocautery (Table 2). It is therefore difficult to implicate the oestrogens in the postoperative LH increase, even if the elevated LH commonly associated with PCO might have a basis in defective oestrogen production.

Since a very high percentage of women with PCO who are treated by ovarian electrocautery go on to ovulate and become fertile with normal levels of gonadotrophins, our observations obviously describe a transitional effect on the endocrine mechanisms. Further studies of the endocrine changes with time after operation might be of interest both for therapy and understanding of the PCO syndrome.

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Received 9 July 1986
Accepted 23 October 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp 784–787

The influence of age on prognosis in carcinoma of the cervix

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Summary. Of 385 new patients with invasive carcinoma of the cervix FIGO stages IB–IV treated between 1970–1984 inclusive, 11% (43 patients) were aged ≤35 years. During the period studied there was a gradual rise in the proportion of such young women from 2% for the triennium 1970–1972 to 18% for 1982–1984. In women aged ≤35 years early stage disease predominated, 72% presenting with stage IB disease, compared with 29% in the older age group. For FIGO stage IB there was no significant difference in actuarial survival between younger and older patients (*P*>0·1), both age groups having a 5-year survival rate of 81%. Similarly for FIGO stage II there was no difference in actuarial survival (*P*>0·1) between younger and older patients who had 5-year survival rates of 66% and 63% respectively. In our experience the incidence of invasive carcinoma of the cervix in young women is rising, but stage for stage their survival is similar to that of older women.

It has been our impression that the incidence of carcinoma of the cervix in young women is increasing and that their prognosis is worse than in older women. The increase in the number of registrations of invasive cancer of the cervix and the rising mortality in young women is well documented (Cook & Draper 1984), but the influence of age on prognosis is controversial and the literature is conflicting. Some authors report that survival is worse in young women (Stanhope *et al.* 1980; Hall & Monaghan 1983), but others report no significant difference in survival between old and young patients (Kyriakos *et al.* 1971; Kjorstad 1977; Bouma & Crane-Elders 1983). In order to clarify this situation, we have analysed our results.

Patients and methods

From 1970–1984 a total of 385 new patients of all ages have been treated at the Royal Marsden Hospital (Sutton) for invasive carcinoma of the cervix (excluding stage IA micro-invasion) and of these 43 patients (11%) were aged ≤35 years at first treament. Patients referred for follow-up or management of recurrence after treatment elsewhere have been excluded. All patients have been referred from two district general hospitals to one radiotherapist (J.W.B.). During this 15-year period there has been a constant referral pattern and treatment policy. The incidence of carcinoma of the cervix in young women (defined as ≤35 years of age) has been calculated by expressing the number of young patients as a percentage of the total number of patients seen in each of five triennia for the 15-year period.

Survival is plotted by the actuarial life table method and the log rank test was used to compare groups and test for statistical significance (Peto *et al.* 1977). To study the effect of age on survival, the actuarial survival for FIGO stages IB and II has been calculated for patients aged ≤35 years and ≥36 years. The number of

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Table 1. Incidence of young patients (aged ≤35 years) with carcinoma of the cervix, The Royal Marsden Hospital, Sutton, 1970–1984

	Carcinoma of the cervix	
Year	Total no.	Young patients (≤35 years) *n* (%)
1970–1972	62	1 (2)
1973–1975	70	5 (7)
1976–1978	81	14 (17)
1979–1981	97	9 (9)
1981–1984	76	14 (18)

Table 2. Distribution of young and old patients in each FIGO stage group

Stage	Age ≤35 years	Age > 35 years
IB	72% (31)	29% (100)
II	21% (9)	29% (97)
III	5% (2)	35% (120)
IV	2% (1)	7% (25)
Total	100% (43)	100% (342)

Number of patients shown in parenthesis.

patients aged ≤35 years with stage III or IV disease was too small for statistical analysis. Patients dying of causes unrelated to carcinoma of cervix or its treatment have been counted as lost to follow-up at the time of death.

Patients were staged using FIGO staging. Initial assessment included chest radiograph, intravenous urography and lymphography, cystoscopy, examination under anaesthetic, dilatation and curettage and biopsy.

Treatment policy

Patients with stage IB, IIA and early IIB disease were treated by two pre-operative caesium insertions, followed by Wertheim's hysterectomy. The intracavitary technique was a modified Stockholm technique using a uterine tube and a single vaginal box, giving 25 Gy to point A in 22 h (Baker 1976). If there were adverse findings, such as positive nodes or doubtful surgical clearance, postoperative pelvic irradiation was given to a dose of 45 Gy in 25 fractions in 5 weeks.

Patients who were unsuitable for surgery had radical radiotherapy with three caesium insertions, each giving 25 Gy to point A, followed by parametrial irradiation, using central lead shielding, giving a total dose of 45 Gy to the parametria.

Patients with stage advanced IIB, III and IV disease were treated with external beam irradiation to the whole pelvis, giving a dose of 45 Gy in 25 fractions in 5 weeks, followed either by a caesium insertion and a boost to the involved parametria of 10 Gy, or by further external beam irradiation to a reduced volume to 60–65 Gy

Results

The incidence of invasive carcinoma of the cervix in women aged ≤35 years, expressed as a percentage of the total number of patients seen in each time period, increased (Table 1) from 2% in the triennium 1970–1972 to 18% in 1982–1984.

The influence of age and stage is summarized in Table 2 and shows that early stage disease predominated in young patients. Of the 43 patients aged ≤ 35 years, 31 (72%) had FIGO stage IB disease, 9 (21%) had stage II disease, 2 (5%) had stage III disease and only 1 (2%) stage IV. Of the 342 patients who were ≥36 years, 29% were stage I, 29% stage II, 35% stage III, and 7% stage IV.

Actuarial survival rates for FIGO stages IB and II are shown in Figs 1 and 2 respectively. There were too few cases of stage III and IV disease for the calculation of actuarial survival rates. The results show that in stage IB, there was no statistically significant difference in actuarial survival between patients aged ≤35 years and those aged ≥36 years, both groups having a similar 5-year survival of 81% (χ^2 0·11, P>0·1). For stage II, the actuarial 5-year survival rates for the older and younger patients were 63% and 66% respectively, which is again not significantly different (χ^2 0·13, P>0·1). For the more recent period 1979–1984, there was a slight trend for a less favourable prognosis in younger women but this was based on only 21 patients and the difference was not statistically significant (P>0·1).

Of the 43 women aged ≤35, 10 have died; two of them had stage III or IV disease, three had stage II and five had stage IB disease. Four of the eight patients who died with stage IB and II

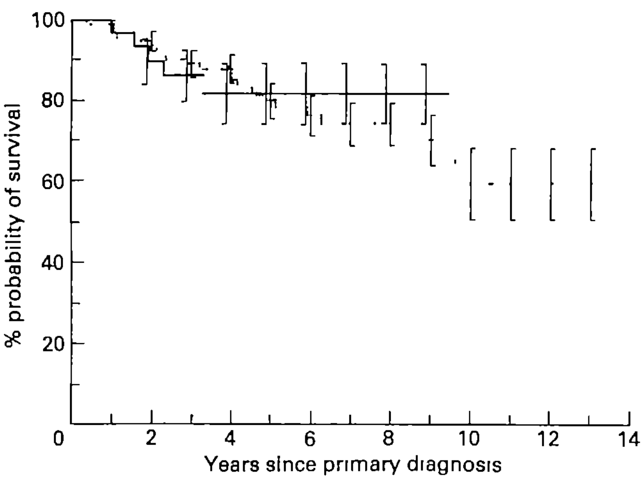

Fig. 1. Actuarial survival of stage 1B carcinoma of the cervix by age. The Royal Marsden Hospital, Sutton, 1970–1984. The vertical bars show the SE values. Death from unrelated causes counted as lost to follow-up at time of death (—) ≤35 years of age (n=31); (--) >35 years of age (n=101). χ^2 0·11, P>0·1.

disease had grossly positive lymphograms and a further patient had a false negative lymphogram with one positive node out of 35 at operation. Although numbers are too small for meaningful 5-year survival rates to be calculated, there is certainly a suggestion that survival is worse in patients with positive lymphograms. Thus 27 of 31 patients with stage I and II and a negative lymphogram are alive, compared with only 3 of 7 who had a positive lymphogram.

Discussion

There is no doubt that the incidence of invasive carcinoma of the cervix and the mortality from this disease are increasing in young women

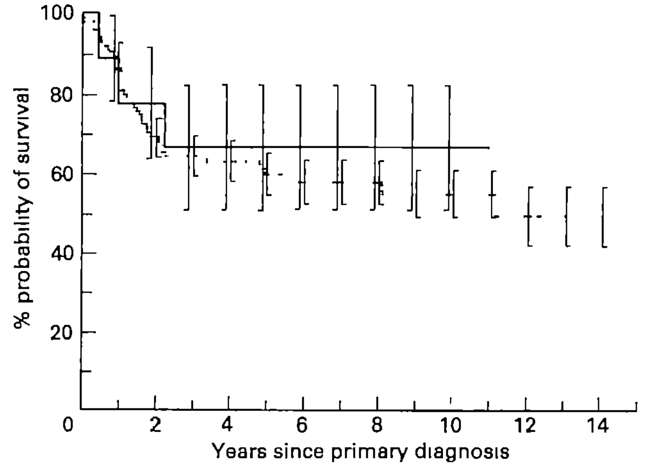

Fig. 2. Actuarial survival of stage II carcinoma of the cervix by age. The Royal Marsden Hospital, Sutton, 1970–1984. The vertical bars show the SE values. Death from unrelated causes counted as lost to follow-up at time of death. (—) ≤35 years of age (n=9); (--) >35 years of age (n=96); χ^2 0·13, P>0·1.

(Cook & Draper 1984), but the influence of age on survival is controversial. Some authors report a worse prognosis in young women (Stanhope *et al.* 1980; Hall & Monaghan 1983), others have found no difference (Kyriakos *et al.* 1971; Kjorstad 1977; Bouma & Crane-Elders 1983), while another report showed prognosis in young women is dependent on type of treatment given (Gynning *et al.* 1983). The death of a young woman from this disease leaves a strong impression on the clinician and it has certainly been our opinion that the prognosis in this age group is worse. However, analysis of our results is not consistent with this opinion and shows that young patients had a more favourable stage distribution than older patients, and stage for stage there was no significant difference in survival.

Although there is a trend for a less favourable prognosis in younger women in the more recent period 1979–1984, this is based on a very small sample of patients with a short follow-up period and the difference is not statistically significant. Clearly a larger group of patients and a longer period of follow-up are needed to see whether difference will become apparent. A national database would clearly be helpful in this respect.

On the basis of these results, we are unable to demonstrate any difference in stage for stage survival between younger and older women, but there is a sub-group of young women who appear to have very aggressive disease and a poor prognosis. As detailed in the results section, the majority of those patients who died had identifiable poor prognostic factors, the most important of which was a positive lymphogram. We have reported similar findings in a larger group of patients of all ages in detail, showing a worse prognosis in patients with lymph node metastases as demonstrated by lymphography (Smales *et al.* 1986). Patients who have apparently early stage disease and a positive lymphogram have a poor prognosis and this subgroup of patients should be considered for more aggressive treatment.

We have also undertaken a study of 191 women aged ≤ 35 years with invasive carcinoma of the cervix at both branches of this hospital, and found that the adverse prognostic features were: stage and bulk of the primary tumour, lymph node metastases by lymphography and grade of histological differentiation (Ashby *et al.* unpublished observations). These are well recognized prognostic features in the disease in general.

In conclusion, we feel that the problem of young women with carcinoma of the cervix is an important one, since the incidence and mortality in this age group is increasing, but the overall picture must be kept in perspective. We would not recommend overall changes in treatment policy for young women on the basis of age alone, as in our experience, many do well with present treatment schedules. The emphasis in the management of young patients, as in patients of all ages, should be on the identification of the poor risk patients and selection of these patients for aggressive treatment.

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Received 30 September 1986
Accepted 24 February 1987

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp 788–790

Recurrent acute leg cellulitis after hysterectomy with pelvic lymphadenectomy

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Summary. Recurrent acute leg cellulitis known to occur in patients with impaired venous or lymphatic circulation was surveyed prospectively in 270 patients after radical hysterectomy with pelvic lymphadenectomy and in 66 patients after hysterectomy with pelvic lymphadenectomy from 1977 to 1985. Among them, six (2%) and three (4%) patients experienced a total of 17 episodes of acute leg cellulitis, respectively. Analysis showed that postoperative percutaneous radiation therapy of the pelvic area was a highly significant risk factor. Penicillin prophylaxis is recommended for patients experiencing recurrent attacks.

Recurrent acute leg cellulitis is characterized by high fever, myalgia, tachycardia and severe prostration. The bacterial cause of the condition is not established. It has been suggested that beta-haemolytic streptococci or bacterial products, bacterial or fungal antigens, eliciting hypersensitivity reactions, are involved (Bisno 1984). Predisposing factors appear to be impaired lymphatic or venous drainage after surgical procedures (Baddour & Bisno 1985) or after irradiation (Gallagher & Algird 1966). The onset of symptoms can occur several months after the operation or after irradiation.

Acute leg cellulitis has been reported in three patients after radical hysterectomy with lymph node dissection followed by radiation therapy (Binnick *et al.* 1980; Chmel & Hamdy 1984). We observed the disease in 33 (26%) of 126 patients after radical vulvectomy (Bouma & Dankert 1987).

In this study we report the prevalence of acute leg cellulitis in patients after radical hysterectomy with pelvic lymphadenectomy and in patients after hysterectomy with pelvic lymphadenectomy. These patients had a lower frequency of the disease than was found in patients after radical vulvectomy.

Patients and methods

Radical hysterectomy

The study included 282 patients with cervical (stage IB or IIa) or endometrial cancer (stage II, macroscopically), admitted from 1977 to 1985, who were treated by abdominal radical hysterectomy with pelvic lymphadenectomy. Cefuroxime and metronidazole were given during and after the operation as antimicrobial prophylaxis for 48 h. Postoperative radiation therapy was given to 67 patients with lymph node involvement or deep myometrial invasion by tumour.

Twelve patients died within one year of surgery so that the occurrence of the disease was studied in 270 patients. The patients were between 18 and 84 years of age (mean 48 years, median 46 years).

Hysterectomy

There were 66 patients with endometrial cancer (stage I, grade 2 or 3) or stage II (microscopically), two patients with uterus sarcoma and one patient with bulky adenocarcinoma of the cervix, admitted from 1977 to 1985, who were

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treated by hysterectomy with pelvic lymphadenectomy. Antimicrobial prophylaxis during and for 48 h after surgery used cefuroxime in combination with metronidazole. Postoperative radiation therapy was given to 31 patients with involved lymph nodes or having deep myometrial invasion by tumour.

Three patients died in the first year after surgery so that the occurrence of acute leg cellulitis was studied in 66 patients. The patients were between 19 and 83 years of age (mean 63 years, median 64 years).

Assessment of acute leg cellulitis

Patients were seen in the out-patients department every 3 months in the first year after operation, in the following years at least twice a year and 5 years after the operation once a year. The onset of symptoms was diagnosed either by patients' family physician or by one of us.

The clinical features of the disease are remarkably similar in affected patients (Baddour & Bisno 1984). There is a sudden onset of fever ranging from 38·5°C to above 40°C, diffuse myalgia, headache and malaise and most of them have rigors. Some hours later a diffuse and flat erythema is seen over the thigh, the inguinal region or the lower abdominal wall. If an attack occurred in an in-patient, the erythrocyte sedimentation rate and leucocyte count were estimated, blood cultures were initiated and blood samples were obtained to determine antistreptolysine (ASO) titres. Two weeks after an attack blood samples were taken again for the determination of ASO titres.

Statistical analysis

The χ^2 test was used for statistical comparison.

Results

Among the 270 patients with radical hysterectomy and pelvic lymphadenectomy, who were surveyed for a total period of 11 942 patient-months, six (2%) experienced 12 episodes of acute leg cellulitis. Three of them had recurrent attacks.

Of the 66 patients with hysterectomy and pelvic lymphadenectomy, who were surveyed for a total period of 2451 patient-months, three patients experienced five attacks, two had recurrent attacks.

Patients with acute leg cellulitis had elevated sedimentation rates and leucocyte counts (range 9000–21 000/μl). Although cultures from the erythematous leg and blood were always negative for beta-haemolytic streptococci, ASO titres in paired serum samples were elevated in approximately 40% of the ill patients.

The first attack occurred an average 29 months after surgery (range 4–52 months). Postoperative percutaneous irradiation of the pelvic area was given to 67 patients who had a radical hysterectomy and 31 hysterectomized patients. Acute leg cellulitis occurred only in those who had had postoperative radiotherapy. There was a highly significant association ($P<0{\cdot}001$) between postoperative radiotherapy and acute leg cellulitis in both patient groups.

Six patients were treated with ampicillin or penicillin during 14 attacks, and general toxic symptoms disappeared within 24 h on each occasion. The erythema and oedema of the leg resolved with desquamation within 5–7 days. In patients not treated with antibiotics, fever and prostration remained for 2–3 days but skin lesions disappeared within a week.

Prophylaxis was attempted in four patients for a total period of 131 patient-months with monthly intramuscular injections of 1·2 million Units of penicillin (Penidural). None of them experienced recurrences during prophylaxis, whereas five patients without prophylaxis had eight recurrences in 73 patient-months.

Discussion

During this prospective survey acute leg cellulitis occurred in six of 270 patients who had radical hysterectomy and in three of 66 patients who had hysterectomies. Recurrences were observed in five of them. Other authors have reported acute leg cellulitis in patients who have had radical hysterectomy with pelvic lymphadenectomy who had several attacks over the years after surgery (Binnick *et al.* 1980; Chmel & Hamdy 1984). All three patients had had postoperative irradiation. It was suggested that the impairment of lymphatic drainage, caused by lymphadenectomy or irradiation or both, predisposes to attacks of acute leg cellulitis. All of our patients had pelvic lymphadenectomy, but attacks occurred only in those treated with radiotherapy. So radiotherapy after hysterectomy with lymphadenectomy significantly increased the risk of acute leg cellulitis. In contrast, radiotherapy did not appear to be a risk factor in patients after radical vulvectomy with inguinal lymphadenectomy (Bouma & Dankert 1987), although the prevalence in this patient group was significantly higher ($P<0{\cdot}001$) than that in patients after hysterectomy with lymphadenectomy. After radical vulvectomy acute leg cellulitis was observed in 33 (26%) of 126 patients in the period between 1973 and 1985 (Bouma & Dankert 1987). In these patients impaired venous drainage due to saphenous venectomy was the probable reason for the development of acute leg cellulitis. In patients who have had coronary bypass graft surgery, recurrent attacks are known to occur in the saphenous vein-donor-leg (Baddour & Bisno 1982; Greenberg *et al.* 1982; Baddour & Bisno 1984).

Patients who have had hysterectomy with pelvic lymphadenectomy differ from those who have had radical vulvectomy as does the interval between surgery and the first attack of acute leg cellulitis. In the former group, the first attack occurred on average 2·5 years after surgery, whereas most of the latter group had their first attack within the first year after operation which further demonstrates the higher susceptibility of patients with radical vulvectomy for this postoperative complication.

The aetiology and pathogenesis of acute leg cellulitis is unknown (Baddour & Bisno 1985). Group A as well as non-group A beta-haemolytic streptococci have been reported in association with the disease (Bisno 1984; Baddour & Bisno 1985). After radical vulvectomy the occurrence of acute leg cellulitis was associated with the perioperative presence of beta-haemolytic streptococci, mainly group B (Bouma & Dankert 1986) but such an association could not be demonstrated in the present series (data not shown). Although ASO titres were elevated in a small number of patients 2 weeks after an attack this finding does not exclude the involvement of beta-haemolytic streptococci in the aetiology of acute leg cellulitis since the antistreptolysine response after cutaneous streptococcal infections is weak (Bisno 1985; Leppard *et al.* 1985). Further evidence that beta-haemolytic streptococci are linked with acute leg cellulitis is shown by the prevention of recurrent attacks by penicillin prophylaxis.

Minor injury to the skin or damage due to Tinea pedis may provide portals of entry for microorganisms, bacterial products or bacterial antigens that may cause acute leg cellulitis (Edwards 1963; Baddour & Bisno 1982, 1985; Greenberg *et al.* 1982). Such lesions were not apparent in any of our patients but special attention to vulvar and foot hygiene is recommended perioperatively and in the years after surgery.

Acute leg cellulitis was sometimes misdiagnosed as thrombophlebitis or septicaemia. Some of our patients were ill enough to require admission to hospital. Specialist surgeons need knowledge of this disease.

Acknowledgments

We are grateful to Mrs B. Hüttenberger for typing the manuscript.

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Received 28 August 1986
Accepted 9 December 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 791–794

Hormonal and ultrasound profile of luteinized unruptured follicle following pulsatile gonadotrophin releasing hormone infusion. Case report

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Case report

A 23-year-old woman presented with a 7-year history of amenorrhoea. Adrenarche and thelarche occurred at age 14, and menarche at age 16. She had had only three menstrual periods during the 7 years since the menarche. Physical examination revealed a healthy woman weighing 58 kg with Tanner 4 breast development. Anosmia, galactorrhea and hirsutism were absent. Pelvic examination was normal. Laboratory results were as follows: luteinizing hormone (LH) 4·7 m-i.u./ml, follicle stimulating hormone (FSH) 4·4 m-i.u./ml, oestradiol (E_2) 12 pg/ml, testosterone 0·40 ng/ml, thyroid stimulating hormone (TSH) 0·84 μ-i.u./ml, thyroxine (T4) 10 μg/dl, prolactin 10 ng/ml, cortisol (at 08.00 hours) 180 μg/dl, and the X cone view of the sella turcica was normal. Release of LH and FSH after a standard administration of 100 μg of LH-releasing hormone (LHRH) was normal. Steroids and gonadotrophins were measured by radioimmunoassay as reported previously (Devoto *et al.* 1980), TSH, T4 and prolactin were measured with commercial kits.

She had no vaginal bleed after withdrawal of administered progesterone and did not ovulate after clomiphene therapy of 150 mg/day for 5 days. Other infertility assessments were normal, including semen analysis, postcoital test, hysterosalpingogram and diagnostic laparoscopy.

A diagnosis of hypothalamic amenorrhoea was made. A positive withdrawal bleed occurred after the administration of oral contraceptives. Beginning day 2 after the withdrawal bleed, LHRH was administered intravenously with a battery-powered time auto infusion pump (Zyclomat, Ferring, W. Germany) at a rate of 10 μg every 90 min as described by Sir-Petermann *et al.* (1984). The solution was infused for 21 days through an heparinized cannula inserted into a forearm vein on an ambulatory outpatient basis. No complications were observed.

Follicular growth was monitored by ultrasonographic measurement of the dominant follicle (PHV sonic alpha I Searle Scanner), clinical assessment of cervical mucus, and daily blood measurements of LH, E_2 and progesterone.

Blood was collected every 15 min during 3 hours in the early follicular phase and at midcycle to study the pulsatile secretion of LH, which was analysed as described by Santen & Bardin (1973).

Results

Figure 1 shows the hormonal profile and ultrasound assessments of the follicular growth in our patient. For comparison the mean (SE) values from nine normal ovulatory menstrual cycles are also shown. All the data were arranged according to the LH peak (day 0).

Until the initial rise of the mid-cycle LH peak there were no substantial differences in gonadotrophins, steroids and ultrasound profile between the normal cycles and the cycle associ-

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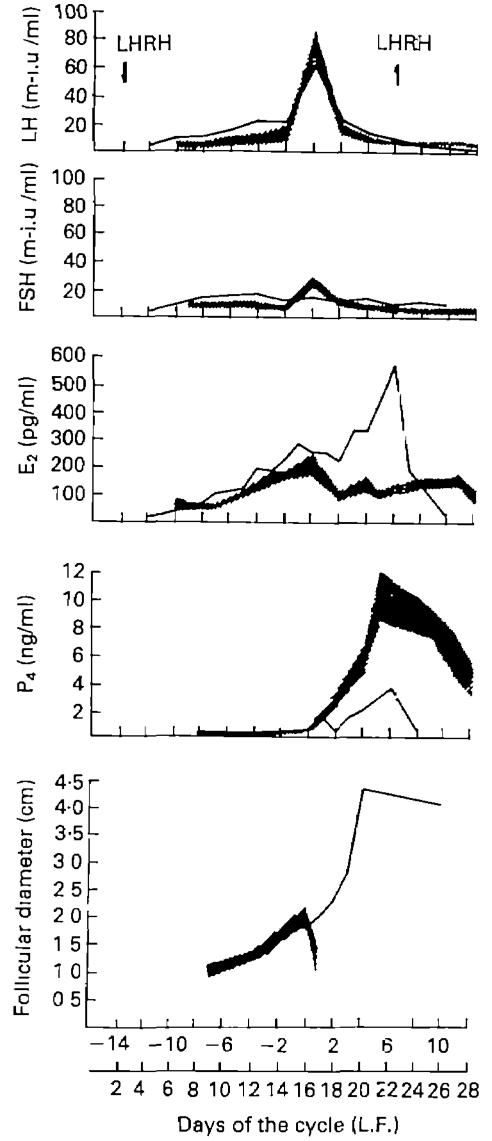

Fig. 1. Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), oestradiol (E_2), progesterone (P) and follicle diameter during a cycle induced with pulsatile LH releasing hormone (LHRH) and associated with a luteinized unruptured follicle. The shaded areas represent the mean (SE) values from nine normal ovulatory menstrual cycles.

ated with luteinized unruptured follicle (LUF). It is interesting to note the absence of an FSH rise at the time of the LH peak, which was also in the low normal range. Simultaneously with the LH peak, a progressive increase (602 pg/ml) in the plasma E_2 level until the day of the pump withdrawal (+6) was noted. On the other hand, the plasma progesterone level was lower than in a normal cycle; the prolactin level was normal during the cycle (data not shown).

The ultrasound profile of the follicular development showed an accelerated growth after the LH peak, reaching a maximum diameter of 4·3 cm at day +6. The decision to stop the LHRH infusion was based on ultrasound evidence of no follicular rupture 120 h after the LH peak.

LH pulses in the early follicular phase and at mid-cycle are shown in Fig. 2. The pulsatility pattern in the early follicular phase showed a normal frequency and amplitude (mean Δ LH=3·5). The mid-cycle LH pulsatility showed a normal increment in the amplitude and a decrease in the frequency (mean Δ LH=7·76) (Reame *et al.* 1984).

Discussion

The LUF syndrome has been characterized by presumptive evidence of ovulation without release of the ovum but its pathophysiology, occurrence and clinical significance have not been established. The standard method of detecting the LUF syndrome has been by laparoscopy and the finding of low levels of progesterone and E_2 in peritoneal fluid (Lesorgen *et al.* 1984).

Recent advances in ultrasound technology have made it possible to assess normal follicular growth, ovulation and to identify follicular rupture (Hamilton *et al.* 1985).

The LUF syndrome has been associated with unexplained infertility, endometriosis, pelvic inflammatory disease (PID) and induction of ovulation, mostly with clomiphene. Little is known about the hormonal profile of the LUF syndrome during induction of ovulation with pulsatile LHRH.

In our patient, the gonadotrophin profile during the follicular phase of the LHRH induced cycle was similar to that seen in normal ovulatory women. Furthermore, the pattern of LH pulsatility in the early follicular phase and at mid-cycle showed normal frequency and amplitude (Reame *et al.* 1984).

Follicular growth in the present LUF cycle, as assessed by cervical mucus production, E_2 secretion and progressive increase in the single dominant follicle, was found to be normal until the LH peak. After this event, a dramatic increase in

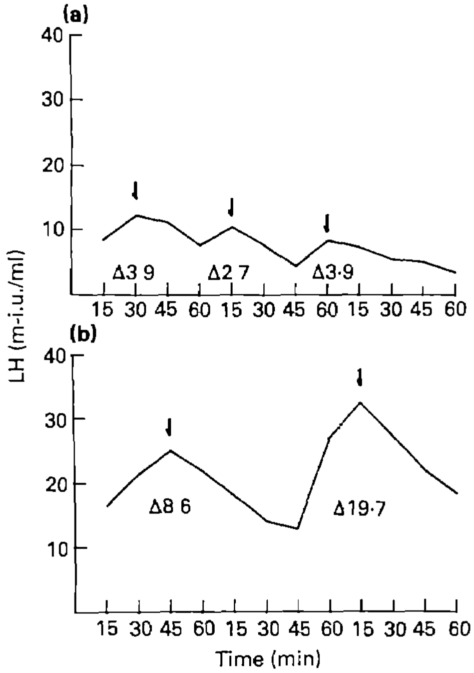

Fig. 2. Luteinizing hormone (LH) pulsatility in the early follicular phase (a) and at mid-cycle (b) during a cycle induced with LHRH and associated with an unruptured follicle. The arrows indicate the LH pulses. (a) E_2:22 pg/ml; P_4:0·03 ng/ml. (b) E_2:252 pg/ml; P_4:0·46 ng/ml.

the follicular volume and E_2 secretion was observed.

These observations are similar to those reported for a series of 20 LUF cycles by Hamilton *et al.* (1985), except that they did not observe a lack of FSH elevation at mid-cycle and a higher E_2 level during the follicular phase.

This higher E_2 level could be explained by the fact that in their study, multiple follicular growth was stimulated with clomiphene or human menopausal gonadotrophin (hMG)—human chorionic gonadotrophin (hCG) regimens. The pathophysiology of the LUF syndrome in our patient is not clear. The absence of endometriosis or PID, as determined by laparoscopy, could exclude in part a local ovarian defect.

An inhibitory effect on progesterone secretion by LHRH agonist in rat granulosa cells and human granulosa cells has been demonstrated (Clayton *et al.* 1979; Tureck *et al.* 1982) but Casper *et al.* (1982) could not confirm the inhibitory effect of LHRH on human granulosa cells. In view of these controversial results no definitive conclusions about the effect of LHRH on gonadal function can be established.

Nevertheless, we emphasize that in our patient, plasma gonadotrophin levels, LH pulsatility, steroid levels, and the ultrasound profile of the ovary were normal during the time of follicular maturation, which makes it difficult to identify the follicle that will fail to rupture. On the other hand, the absence of FSH increase at the time of mid-cycle LH peak, which was also in the low normal range, suggests that a central disturbance in gonadotrophin release is associated with the pathogenesis of the unruptured follicle.

Acknowledgments

The authors wish to thank Dr F. Cassorla from NIH, Bethesda, Maryland, USA, for helpful discussion; Enriqueta Goubet for typing the manuscript and the National Pituitary Agency NIAMDD for providing the reagents for LH-FSH assays.

This work was supported in part by a grant from Deutsche gesellschaft fur Technische Zusammenarbeit, GmBH and by Fondecyt (Grant 0509/85).

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Received 24 July 1986
Accepted 19 November 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 795–797

Carcinoma developing in bladder exstrophy. Case report

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Case report

A 55-year-old woman with bladder exstrophy was admitted to the Department of Obstetrics and Gynecology of the University of Pisa. She underwent medical examination for this disorder only during adolescence but no adequate treatment was undertaken. She did not remember any noteworthy infections of the urinary tract, and at the time of admission renal function was normal. Examination revealed the presence of a round, irregular, friable, ulcerated mass, measuring 9 cm in diameter, in the hypogastric region (Fig. 1). Below this mass a vestige of the inferior part of the labia remained, while the clitoris was absent. Two halves of the mons veneris were displaced laterally, to the inguinal regions. Bilateral inguinal hernia was observed. The umbilicus was absent. An injection of methylene blue showed the ureteral orifices near the base of the exstrophic mass on either side of the mid-line, slightly above the structures that seemed to belong to the genital tract. Histological examination of two biopsies revealed a signet-ring cell carcinoma. Pelvic X-ray showed diastasis of the symphysis. Urography demonstrated the dilated ureters terminating separately on the abdominal wall. Lymphography showed metastatic involvement of bilateral inguinal lymphnodes. Surgical removal *en bloc* of the exstrophic mass, the uterus, the adnexa and the rudimentary patch of the vagina was performed, together with bilateral ureterosigmoidostomy. A bilateral inguino-iliac lymphadenectomy was also undertaken. Pathological examination confirmed the diagnosis of signet-ring cell carcinoma with metastasis in inguinal lymphnodes. Figure 2 shows a diffuse infiltration by signet-ring cells.

In the bladder several types of epithelium were seen (Fig. 3). In some areas hyperplastic mucosa of colonic type was found. Alcian blue at pH 1 and pH 2, and PAS alone and PAS after diastase, demonstrated intracellular mucin in the signet-ring cells and in the mucosa of the colonic type. An immunoperoxidase study of the neoplastic signet-ring cells with antibodies to carcino-embryonic antigen (CEA) showed a strong positivity in the residual thin ring of cytoplasm. CEA was also present on the luminal surface of normal and hyperplastic cells in the mucosa of colonic type. Postsurgical high energy radiotherapy was carried out (45 Gy). One year after the patient is free of disease.

Discussion

Exstrophy of the bladder is a rare congenital defect caused by an incomplete fusion of the mesoderm that forms the genital tubercles, the anterior wall of the urinary bladder and the lower portion of the anterior wall of the abdomen. The posterior bladder wall, therefore, opens into the hypogastric surface of the abdomen (Pugh 1977). If this congenital malformation is not corrected in childhood, death may occur because of pyelonephritis (Yannopoulos & Kyriakidis 1979). A possible occurrence is neoplastic degeneration, and to 1983, 81 cases of

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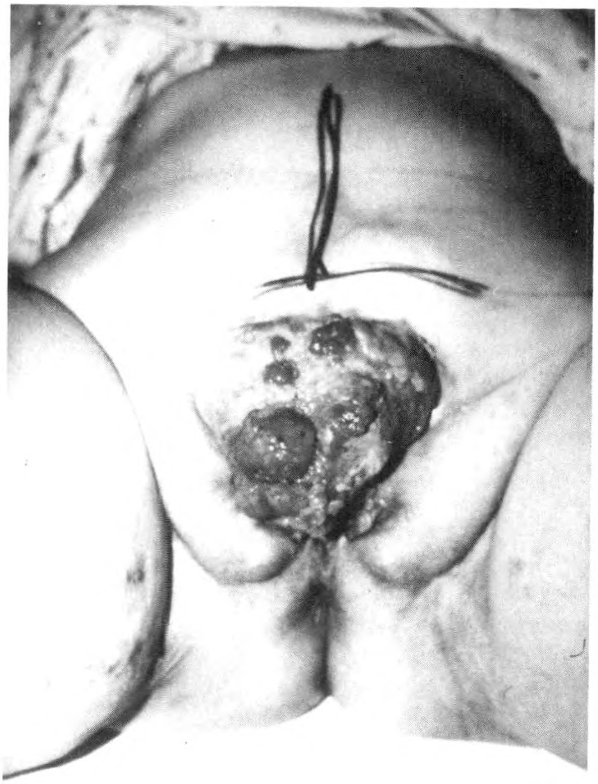

Fig. 1. Neoplasia of exstrophic bladder. Presurgical aspect.

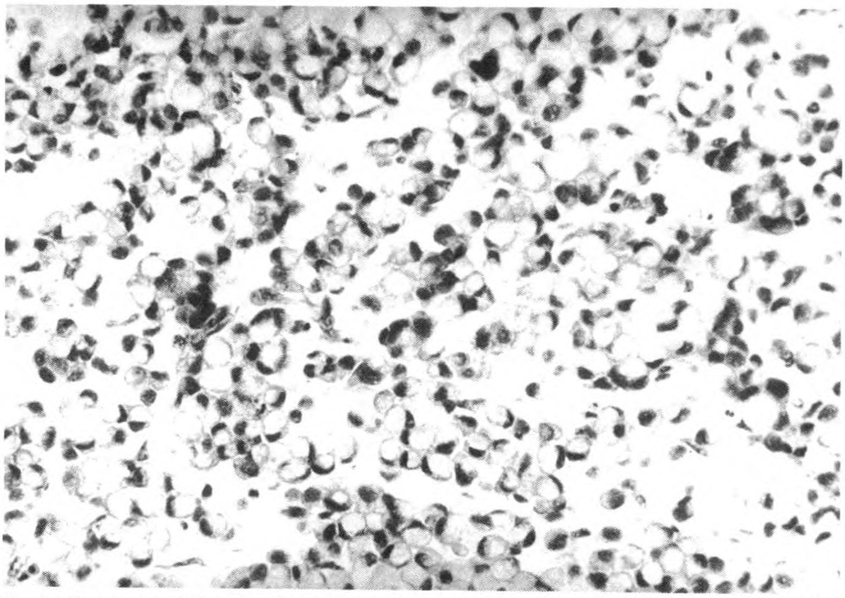

Fig. 2. Characteristic feature of the neoplasia: numerous signet-ring cells, with nuclei pushed peripherically by intracellular mucus.

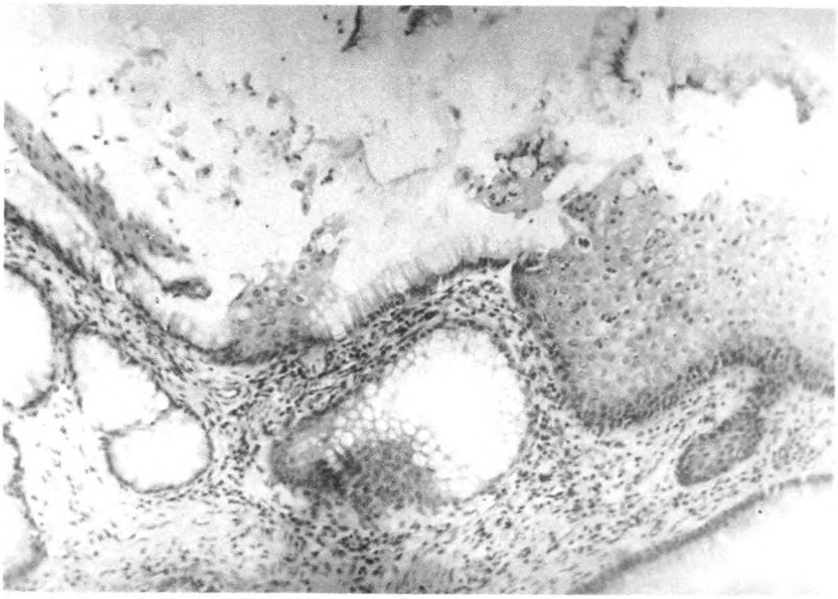

Fig. 3. Area of vesical mucosa: columnar epithelium of intestinal type and cutaneous squamous epithelium.

carcinoma in exstrophic bladders were described in the literature (Culp 1964; Nataf & Liberman 1971; Nielsen & Nielsen 1983).

Whereas 80% of vesical tumours in the general population are transitional cell carcinomas, 95% of the neoplasias developing in exstrophic bladders are adenocarcinomas (Marten-Perolino & Mariano 1983). In our patient the signet-ring cell carcinoma showed strong positivity for Alcian blue and PAS in the intracytoplasmic vacuoles and for CEA in the peripheral areas of the cytoplasm. The normal and hyperplastic mucosa of colonic type retained mucin production and showed positivity for CEA on the luminal surface of the cells. It seems that adenocarcinoma in an exstrophic bladder originates from the colonic epithelium covering the mucosa of the organ (Nielsen & Nielsen 1983). The intestinal type epithelium could derive from a metaplastic process, or could be of ectopic origin (Culp 1964).

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Received 22 April 1986
Accepted 17 October 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 798–802

Placenta membranacea. Case reports

VICTOR A. HURLEY, NORMAN A. BEISCHER

Case reports

Patient no. 1

A 34-year-old Caucasian woman presented at 15 weeks gestation in her fifth pregnancy in 1980. She had had one normal vaginal delivery, two first trimester terminations of pregnancy, and a pregnancy complicated by placental abruption at 36 weeks gestation. She had an uncomplicated antenatal course until 30 weeks when growth of the fetus was considered suboptimal clinically; an ultrasound scan showed growth within the normal range for gestational age and a placenta lying on the anterior and left lateral walls. At 33 weeks she presented with bright, painless vaginal bleeding of approximately 50 ml. A further ultrasound scan again demonstrated the placenta to be on the anterior and left lateral walls. No placenta was identified encroaching on the lower uterine segment or over the cervix on specific cervical views. The fetal biometry at this time suggested normal fetal growth. She was admitted to hospital and no further bleeding occurred before she was discharged 72 h later. Further bright, painless vaginal bleeding of 200 ml occurred at 35 weeks gestation and she was readmitted. Urinary oestriol excretion was low but cardiotocography was normal. When bright vaginal bleeding continued during the subsequent 48 h, surgical induction of labour was performed together with oxytocic augmentation. After 5 h of labour, a further blood loss of about 150 ml occurred. Vaginal examination revealed full cervical dilatation and a left occipito-posterior position. Manual rotation was performed followed by a Neville–Barnes forceps delivery. A female infant weighing 2235 g was born with Apgar scores of 5 at 1 min and 8 at 5 min.

The placenta was retained and manually removed under epidural analgesia. Examination of the placenta showed it to be a placenta membranacea with villous tissue forming a complete shell around the gestation sac. It weighed 470 g and was of uniform thickness measuring between 2 and 3 cm throughout. Total blood loss in the second and third stage of labour was estimated to be 600 ml. The patient was transfused with 2 units of blood.

Patient no. 2

A 23-year-old Asian woman in her first pregnancy was seen at 25 weeks gestation in 1984. At 30 weeks gestation a breech presentation and polyhydramnios were suspected clinically; ultrasound examination showed a normally grown fetus for gestational age, mildly increased amniotic fluid volume and a large thin placenta covering the internal cervical os (Fig. 1). The placenta was also noted to be covering the anterior, posterior and left lateral walls (Fig. 2). The diagnosis of placenta praevia type IV was made and the patient admitted to hospital where she remained until delivery. There was no fresh vaginal bleeding although there were two recorded episodes of dark spotting 2–3 weeks after admission. She was ultimately delivered at 36 weeks gestation by lower uterine segment caesarean section of a male infant weighing 2630 g with Apgar scores of 7 at 1 min and 8 at 5 min; it then became obvious that placental villous tissue lined the entire uterine cavity. The diagnosis was confirmed after delivery of the placenta when villous tissue was seen to cover the entire surface of the membranes (Fig. 3). The placenta weighed 590 g and was between 1 and 3 cm in thickness throughout. The placenta was thickest in the area adjacent to the cervix

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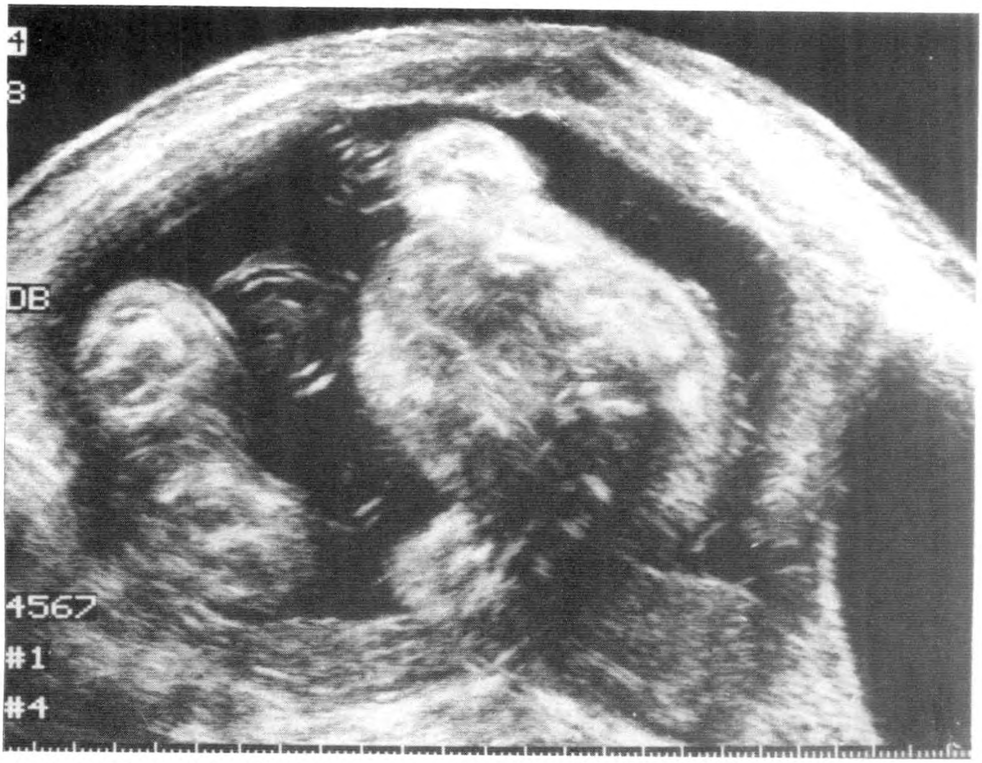

Fig. 1. Patient no. 2. Longitudinal sonogram of the uterus at 30 weeks gestation clearly demonstrating placenta covering the internal cervical os but failing to demonstrate convincingly it in the uterine fundus.

and thinned progressively towards the fundus of the uterus. Blood loss at delivery was estimated to be 500 ml.

Patient no. 3

A 22-year-old Caucasian woman was transferred from a regional hospital in 1985 at 30 weeks gestation in her third pregnancy with the diagnosis of placenta praevia type II and continuous vaginal bleeding. Her history consisted of a first trimester termination of pregnancy followed by a spontaneous first trimester abortion. Her antenatal course had been complicated by five episodes of bright, painless vaginal bleeding between 26 and 30 weeks gestation. The placenta was reported as being on the left lateral wall extending onto the anterior and posterior walls and down to the level of the internal cervical os on an ultrasound scan performed at 27 weeks gestation. Ultrasound scans at 30 and 32 weeks gestation reported the placenta to be on the right lateral and anterior walls. Difficulty was encountered in seeing the lower uterine segment posteriorly due to shadowing from the fetal skull and it was not possible to exclude entirely a minor degree of placenta praevia. She remained in hospital for 1 month. After discharge, the pregnancy was managed in the antenatal clinic until spontaneous rupture of membranes at 37 weeks gestation. After a labour lasting 5 h, the patient was delivered vaginally of a male infant weighing 3520 g with Apgar scores of 6 at 1 min and 8 at 5 min. The placenta was delivered by controlled cord traction and examination revealed a placenta membranacea with villous tissue completely covering the surface of the membranes. The placenta weighed 790 g. The thickest portion of the placenta to which the cord was attached had been situated on the left lateral uterine wall. Total blood loss in the second and third stages of labour was 600 ml. The haemoglobin level after delivery was 6·2 g/dl and the patient was transfused with 4 units of blood.

Discussion

Placenta membranacea or placenta diffusa is a rare developmental anomaly of the placenta where all, or most of, the membranes are covered by chorionic villi. It represents a persistence of the trophoblastic shell without the

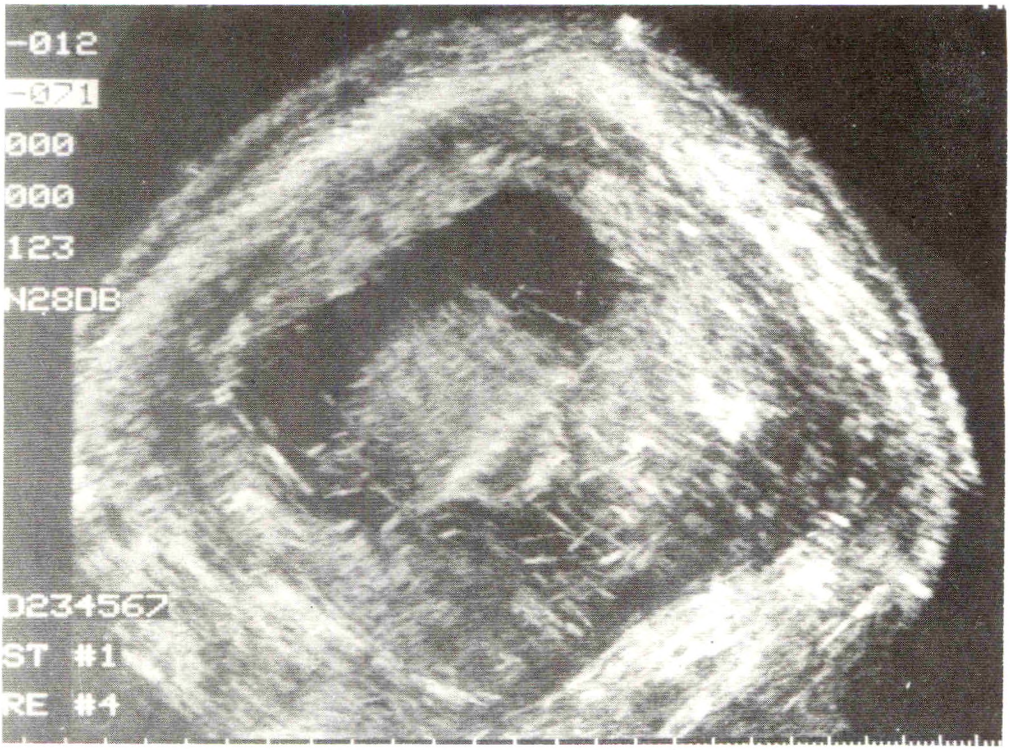

Fig. 2. Patient no. 2. Transverse sonogram of the uterus at 30 weeks gestation demonstrating placenta lining the uterine cavity.

usual differentiation into chorion frondosum and chorion laeve which normally occurs by the 8th–10th week of gestation (Fox 1978). It is the normal form of placentation throughout pregnancy in the pig, donkey and elephant.

The frequency of placenta membranacea is quoted as 1 in 3300 deliveries (Janowski & Granowitz 1961). The present report describes three patients with placenta membranacea encountered at the Mercy Maternity Hospital in the 15-year period from 1971 to May 1986 during which time there were 64 460 confinements and 553 cases of placenta praevia. Scrutiny of all 553 case records of patients with placenta praevia managed during this time revealed no other instances of placenta membranacea. The incidence of placenta membranacea in our population is therefore 1 in 21 500 deliveries and 1 in 184 cases of placenta praevia.

The aetiology of placenta membranacea is not known although factors such as previous endometritis, poor development of a decidual blood supply, unduly deep implantation of the ovum, and atrophy or hypoplasia of the endometrium have been cited as possible factors (Pryse-Davis *et al.* 1973). Two of our three patients had a history of first trimester suction termination of pregnancy but no other risk factor was identified. Recurrent bleeding in the late first and second trimesters, often leading to spontaneous abortion or premature labour, has been previously reported as the most common presentation of placenta membranacea (von Weiss 1894; Finn 1954; Pryse-Davis *et al.* 1973; Culp *et al.* 1973). In our three patients no first trimester bleeding occurred and in patient no. 2 there was no fresh bleeding before abdominal delivery although some dark spotting had been reported.

These three cases are also unusual, compared with previous case reports, in that all three resulted in delivery in the third trimester with favourable fetal outcomes. It is remarkable that two of three patients (patients nos 1 and 3) were delivered vaginally with an estimated blood loss of only 600 ml. A review of the literature revealed only six cases of a successful fetal outcome in a pregnancy complicated by placenta membranacea (De Lee 1902; Aguero 1957; Culp *et al.* 1973; Molloy *et al.* 1983); the most frequent outcome of these pregnancies was premature delivery in the second trimester usually associated with heavy bleeding. These pregnancies are

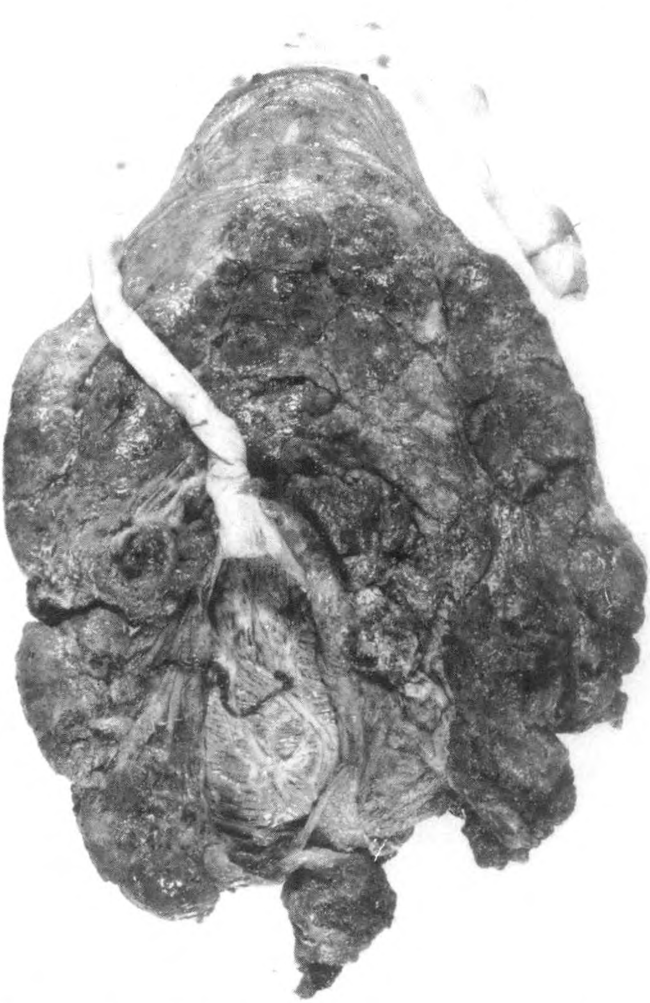

Fig. 3. Patient no. 2. Placental villi cover almost the entire surface of the membranes. The incision made through the placenta at caesarean section is also shown.

thus similar to those complicated by type IV placenta praevia.

It seems possible from our patients that the position of the area of placenta associated with the origin of the umbilical cord relative to the cervix is a significant determinant of outcome. In both the vaginal deliveries (patients nos 1 and 3) the cord insertion was well away from the cervix. The decidua furthest from the origin of the cord may well be less vascular and heavy bleeding may not result when placental tearing and/or separation occurs in labour. Perhaps when the placenta is thin the head engages in labour and exerts pressure on it thus minimizing bleeding when the inevitable damage to the placenta occurs.

Other clinical features reported in association with placenta membranacea include adherent or retained placenta (as occurred in patient no. 1), postpartum haemorrhage and intrauterine growth retardation (von Weiss 1894; De Lee 1902; Finn 1954). All three infants in this study had birthweights above the 10th centile for gestational age for our population.

The antenatal diagnosis of placenta membranacea presents a particular challenge to the ultrasonographer and in only two patients reported in the literature was the diagnosis made before delivery of the fetus. In one of them, diagnosis at 20 weeks gestation was followed by spontaneous vaginal delivery of a stillborn infant at 26 weeks gestation (Wladimiroff *et al.* 1976) and in the other, diagnosis at 27 weeks gestation was followed by classical caesarean section three weeks later because of an episode of haemorrhage. This infant weighed 1100 g and survived (Molloy *et al.* 1983). In two other reports, the diagnosis was made on retrospective examination of ultrasonographs (Pryse-Davis *et al.* 1973) and arteriograms (Culp *et al.* 1973).

Where the placenta is uniformly distributed over the membranes and a reasonable thickness of tissue is maintained, it should be easily seen on ultrasound examination. However, as demonstrated in all our three patients, the thin placenta membranacea stretched over the surface of the expanded gestation sac may elude identification. Reported cases stress the formation of a distinct placental disc in the region of the cord insertion with progressive thinning of the placental substance away from it. Where the disc is seen, particularly if in the fundus, the ultrasonographer may be less vigilant in examination of the lower segment and the internal cervical os thus missing the thin distal portion of the placenta. This serves to underline the necessity, particularly in patients with antepartum haemorrhage, of specific examination of the internal cervical os area, even where the placenta is apparently well away from it. Other conditions significant in this context which may lead to a false negative diagnosis of a low lying placenta, include bilobate or multilobate placentas and succenturiate placental lobes. In cases where difficulty is encountered due to shadowing behind the fetal head, and simple manipulations such as full bladder, head down tilt and gentle abdominal manipulation are not successful in moving the fetal head, the use of vaginal transducers or magnetic resonance imaging may enable accurate diagnosis.

Acknowledgment

We wish to thank our colleagues for their co-operation in this study.

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Received 7 August 1986
Accepted 15 October 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp 803–806

Untreated homocystinuria: a maternal death in a woman with four pregnancies. Case report

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Case report

The patient, who was diagnosed to be homozygous for homocystinuria at 11 years of age in 1967, had four pregnancies between 1975 and 1985. She had been lost to follow-up since 1974, and was never treated, the condition being unrecognized in her first two pregnancies. In 1961 surgical correction for dislocated lenses had been performed.

Her first pregnancy in 1975 when she was 18 years of age ended in a premature stillbirth at 28 weeks gestation; the baby weighed 1180 g. An activated partial thromboplastin time performed at this time was within the normal range.

The second pregnancy in 1983 ended in a spontaneous abortion at 10 weeks gestation.

The patient was pregnant for the third time at 27 years of age in 1984. Caesarean section was performed at 31 weeks gestation for intrauterine growth retardation and fetal distress. The baby weighed 930 g and survived. Postoperatively she was treated with anti-embolic stockings and a 7-day course of subcutaneous heparin. There were no problems in the puerperium.

In 1985 at 28 years of age she booked at 17 weeks gestation in her fourth pregnancy and was seen regularly to 29 weeks gestation. At this visit intrauterine growth retardation was suspected clinically and confirmed by ultrasound scan. Hypertension without proteinuria was also noted. Antenatal cardiotocography suggested fetal compromise, and therefore an emergency lower segment caesarean section was performed under general anaesthesia. The newborn infant weighed 970 g and died a week later. Autopsy showed the cause of death to be necrotizing enterocolitis, secondary to thrombosis of the left umbilical artery extending to the aortic origin of the coeliac axis. This was thought to have been initiated by the presence of an umbilical artery catheter.

Postoperatively no special precautions were taken. The patient developed a wound infection, which was treated successfully with amoxycillin/clavulanic acid and was discharged home after 7 days.

Two weeks later she was admitted unconscious and having grand-mal fits. Although she became semi-conscious later, she was aphasic and disoriented. Neurological examination at this stage revealed bilateral brisk reflexes only.

On the next day she started to have focal convulsions, and a CT scan revealed a right sided parietal lesion suggestive of a haemorrhagic infarct. In view of this dexamethasone was added to her anticonvulsant therapy.

Despite these measures her level of consciousness deteriorated over the ensuing 24 h and her diastolic blood pressure rose to over 140 mmHg.

On the fourth day after admission she had a prolonged apnoeic attack. This was managed by intubation and positive pressure ventilation. Shortly after this she developed ventricular fibrillation unresponsive to treatment, followed by asystole and death.

Autopsy revealed extensive adherent thrombus in the superior sagittal sinus and the cortical veins. The cerebral arteries were mildly atherosclerotic, as were the aorta and main branches.

Discussion

Homocystinuria is a rare inborn error of amino acid metabolism, which is inherited in an autosomal recessive manner. It occurs in about 1/200 000 of the population of mainland Britain

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with an estimated heterozygote frequency of 1/70 to 1/200.

In the commonest form, the normal pathway of conversion from methionine to cysteine is disrupted by a deficiency of the enzyme cystathionine synthase. This results in accumulation of the intermediate product homocysteine and its reversible conversion to methionine.

This biochemical imbalance produces a weakening of collagen linkages, and the clinical manifestations of mental retardation, ectopia lentis, thrombotic episodes and skeletal/connective tissue abnormalities which are almost identical to Marfan's syndrome (Mudd & Levy 1983).

The condition has variable clinical expression and is probably under diagnosed. However, once the diagnosis is made, most patients receive good follow-up care and appropriate treatment. Homocystinuria due to cystathionine synthase deficiency can be classified according to response to pyridoxine. Pyridoxine is a co-enzyme for the conversion of homocysteine to cystathionine, and approximately 40% of cases respond to pharmacological doses (approximately 500 mg/day) (Mudd & Levy 1983).

A well-documented clinical response to this simple treatment is recorded. In particular, thrombotic episodes, other complications and mortality can be reduced or delayed (Mudd *et al.* 1985). In the non-responders other treatments are possible; these include low methionine diets, betaine, choline and anti-thrombotic measures.

Several reports detailing pregnancies in women with homocystinuria have been published (McKusick *et al.* 1971; Ritchie & Carson 1973; Brenton *et al.*, 1977; Drayer *et al.* 1980; Kurczynski *et al.* 1980; Newman & Mitchell 1984). These and others have been reviewed previously (Lamon *et al.* 1981; Mudd & Levy 1983), and recently a major international survey of 629 patients has examined the natural history of homocystinuric patients and the progression of their disease (Mudd *et al.* 1985).

This has confirmed the high incidence of thrombotic episodes in patients with homocystinuria, and also that postoperative thromboembolic complications are commoner in this population. Their data suggested that treatment with pyridoxine reduced the likelihood of thromboembolic episodes and delayed their onset. This survey reported 108 pregnancies throughout the world in 47 women. Six were terminated by elective abortion, leaving 102 for assessment. The results in pyridoxine responsive women (79 pregnancies) indicated a fetal loss for the untreated group of 48% compared with 26% for the treated group. These data agree with earlier reports. Three women however, severely influenced these results, as between them they had 24 pregnancies, mainly unsuccessful. If these latter pregnancies are eliminated, there is no statistical difference between the treated and untreated groups, suggesting that treatment does not affect the outcome.

Two thrombotic episodes associated with pregnancy are described. One woman developed an ileo-femoral thrombosis in the puerperium despite anti-platelet treatment (Lamon *et al.* 1981) and the other developed multiple arterial thromboses in the puerperium (Newman & Mitchell 1984). We are not aware of any maternal deaths or caesarean sections being recorded in the literature.

Our case illustrates several features. Whilst we cannot be certain that our patient had no other condition predisposing her to thrombotic episodes, a normal partial thromboplastin time makes the presence of lupus anticoagulant highly unlikely. None of the four pregnancies in our patient was normal. One ended in a premature stillbirth, another in spontaneous abortion and two in caesarean section for fetal distress at around 30 weeks gestation. It is difficult to draw conclusions from one patient, but this seems at variance with the data previously reported. Some cases did have a poor obstetric history (Mudd *et al.* 1985), but most of these women had spontaneous abortions rather than problems in later pregnancy. We would, therefore, still suggest that untreated maternal homocystinuria may increase both the maternal and fetal risk.

The thrombotic tendency of pregnancy and the puerperium is exacerbated by that of homocystinuria. In addition, due to folate depletion and depleted levels of pyridoxine (Wachstein *et al.* 1957; Rose & Braidman 1971; Morrow & Barnes 1972) pregnancy tends to exacerbate homocystinuria.

Sagittal sinus thrombosis is well recognized in association with pregnancy (Carrol *et al.* 1966), but has only been recorded in children with homocystinuria previously (Gibson *et al.* 1964; Hopkins *et al.* 1969).

The occurrence in our patient is especially worrying when the causal factor is potentially treatable and when a previous caesarean section covered by anti-coagulants had been uneventful.

Two important points can be made. It is apparent that obstetric and anaesthetic staff in general are not cognisant with this condition. This may apply to other similarly rare conditions, and should act as a warning when such patients present. The first essential therefore is to be aware of the condition and its potentially lethal consequences.

Specific treatment should be given during the pregnancy, and measures taken to avoid thrombosis. A controlled trial would be needed to assess fully the efficacy of treatment, but is impossible due to the small number of patients with the condition.

Pyridoxine (if a responsive variant) may help the pregnancy outcome, and certainly decreases the maternal risk. Careful monitoring of folate and vitamin B12 levels, and their supplementation, is also required (Ritchie & Carson 1973). There is no recorded experience with low methionine diets, or betaine/choline therapy in pregnancy, and their use cannot be recommended. Similarly results using aspirin and dipyridamole during pregnancy are inconclusive. This therapy may be useful in the puerperium, however.

Our main recommendation would be that specific measures to avoid thrombosis at delivery and in the puerperium are instituted, especially following operative delivery. Avoidance of dehydration and rapid mobilization are important. Care must be used with epidural and spinal anaesthesia as peripheral vasodilatation and vascular stasis can occur (Parris & Quimby 1982), and the anaesthetist should be made aware of the maternal condition. Dextran 40 reduces platelet adhesion and should be given at the time of operation. Compression stockings and inflatable leggings may also be useful.

Postoperatively or in the postnatal period, subcutaneous heparin should be considered, certainly until full ambulation is achieved and probably until the effects of pregnancy on the clotting mechanism have ceased. Pyridoxine therapy should be continued, and a low methionine diet considered in certain cases.

If wound infection develops, or after a normal delivery endometritis, further care is required as this may be a possible source of septic emboli or septicaemia, said to be precursors of cranial sinus thrombosis.

In summary, this case highlights the importance of being aware of this condition and its possible consequences, and thus being in a position to institute special precautions and prophylactic measures. The clinical features of homocystinuria may be very mild and consequently the disorder may go undiagnosed. Patients with unexplained lens dislocation or previous thromboembolic disorder, especially if associated with developmental retardation, Marfanoid features, seizures, or behavioural disorders, should be investigated for this condition.

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Received 18 August 1986
Accepted 17 October 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 807–810

Postpartum hyperparathyroid crisis. Case report

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Case report

The patient was a 34-year-old white woman in her second pregnancy. In 1978 she had an uneventful pregnancy which ended in vaginal delivery of a live male baby at term. In 1982 she developed a diffuse swelling of the left lobe of the thyroid gland. She was clinically and biochemically euthyroid. A thoracic inlet X-ray showed that the trachea was deviated to the right but radioactive iodine scanning showed no evidence of retrosternal thyroid prolongation. She remained euthyroid and the swelling eventually subsided. She was discharged from the medical follow-up clinic a few months before her current pregnancy.

The patient attended the booking antenatal clinic at 13 weeks gestation and no thyroid swellings were noticed. Apart from general weakness and lack of energy during the last few weeks of pregnancy, she had never had any specific complaints. Her blood pressure had always been within normal limits and urinalysis had never shown any abnormality.

At 39 weeks polyhydramnios was noticed. A glucose tolerance test was within normal limits. An ultrasound scan and X-ray did not show any fetal abnormality. She was admitted for rest at 40 weeks as she looked excessively weak. On the following day she went into spontaneous labour which progressed normally. The second stage ended with a low forceps delivery because of lack of maternal effort. A healthy baby weighing 3.070 kg was born.

Postpartum, the mother developed progressive weakness, nausea and looked ill. No abnormality was detected on examination and her haemoglobin was 12·5 g/dl. It was only on the third postpartum day that parathyroid and renal function were investigated. She was found to be grossly hypercalcaemic with poor renal function (serum calcium: >5 mmol/l, phosphates: 1·9 mmol/l, albumin: 28 g/l, urea: 23·5 mmol/l). X-ray of her hands showed subperiosteal resorption, with small cystic lesions and skull X-ray showed a classical pepper pot appearance with resorption around the teeth. A diagnosis of primary hyperparathyroidism was confirmed. Her general condition deteriorated very rapidly and she became very ill with increasing weakness and confusion and also developed upper abdominal pain and respiratory difficulties. Before referral to the regional centre for surgical exploration of the parathyroids, attempts were made to lower serum calcium medically with slight success. Intravenous fluids including albumin were given in addition to frusemide, hydrocortisone and phosphates.

At the time of transfer on the fourth postpartum day, she was confused with short lucid intervals. There was hypotension, acidosis, and renal function was very poor in spite of treatment. In addition, there was progressive respiratory distress. Haemodialysis was carried out and intermittent positive pressure ventilation was commenced. In spite of initial improvement, her condition suddenly deteriorated with gross distension of the abdomen. Neck exploration was performed on the fifth postpartum day with removal of a large parathyroid tumour from the left pole of the thyroid gland. Concomitant laparotomy because of the gross distension of the abdomen, persistent free gas on X-rays and rapidly deteriorating condition of the patient revealed only uncomplicated acute pancreatitis and drainage was effected. Immediately after the operation her condition was more stable but on the following day she went into terminal shock from which resuscitation was unsuccessful.

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Pathological examination

The surgically-excised left parathyroid gland weighed 31 g and measured 6 × 3·5 × 3·5 cm (Fig. 1). The cut surface showed small haemorrhages and histological examination revealed a chief cell adenoma with both recent and organizing thrombi in many vessels (Fig. 2). At necropsy two normal parathyroid glands were identified. The cause of death was adult respiratory distress syndrome due to a combination of acute necrotizing pancreatitis and renal failure. Bilateral renal vein thrombosis was present and histologically there were thrombi in glomerular capillaries (suggesting disseminated intravascular coagulation) together with tubular calcification and extensive interstitial fibrosis around tubules and glomeruli. Metastatic calcification was also seen in the myocardium, pulmonary vessel walls and bronchial walls. Two small pulmonary thromboemboli were thought to have arisen from the renal vein thrombus. Samples of rib, skull and iliac crest all showed florid parathyroid bone disease. There was no evidence of infection or amniotic fluid embolism.

Discussion

Hyperparathyroid crisis is characterized by rapidly progressive nausea, vomiting, lethargy, profound muscle weakness, mental confusion, progressive uraemia and ultimately death (Thomason *et al.* 1981). There is rapid elevation of serum calcium levels above 3·74 mmol/l and coma may supervene above levels of 4·99 mmol/l (Thomas *et al.* 1979). Only two cases of post-partum hyperparathyroid crisis have been reported (Schenker & Kallner 1965; Salem & Taylor 1979). In three other cases hyperparathyroid crisis occurred in the third trimester (Whalley 1963; Clark *et al.* 1981; Thomason *et al.* 1981). Hyperparathyroidism in pregnancy is a very rare condition which has been reported in fewer than 100 cases to date (Shangold *et al.* 1982; Pitkin 1985). It is associated with a high rate of fetal loss and increased perinatal morbidity and mortality (de Swiet 1984). There is also increase in maternal morbidity and even, in severe cases, mortality (Schenker & Kallner 1965).

Hyperparathyroidism is usually a slow progressive disease that may remain asymptomatic until the hypercalcaemia is severe. Frequently the disease, as in our patient, presents with vague and non-specific symptoms that could be attributed by the patient and probably her attendants to the pregnancy itself. We wonder if our patient had hyperparathyroidism since early in pregnancy. In fact, the condition might have existed since the enlargement of the left thyroid lobe was observed well before the current pregnancy which could just have been due to haem-

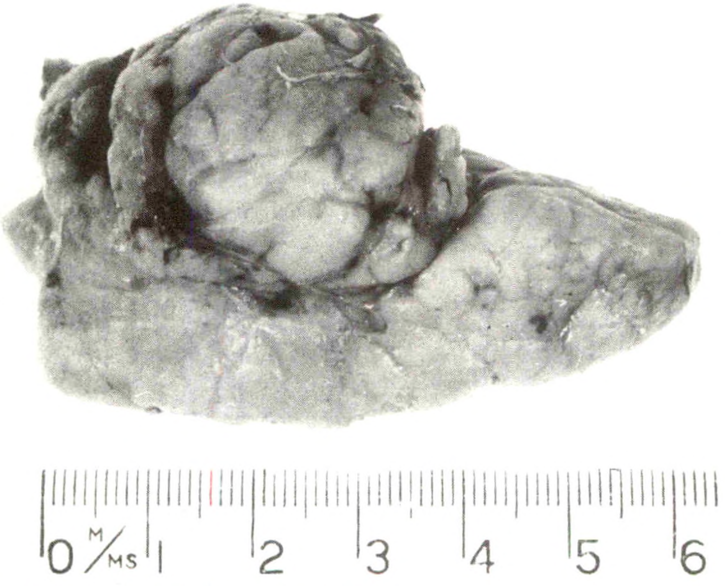

Fig. 1. Surgically-excised adenoma × 1·5.

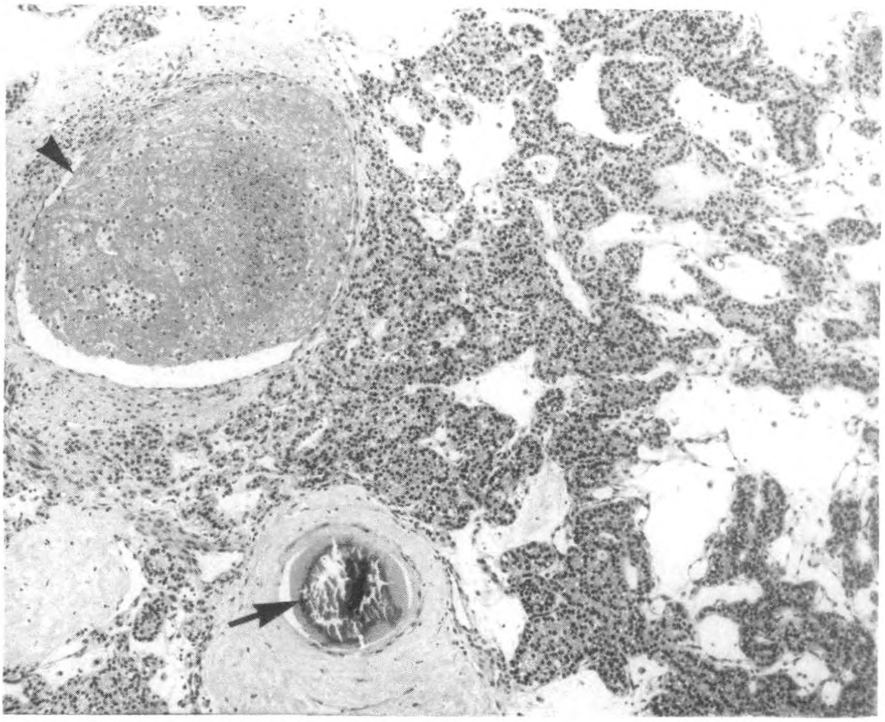

Fig. 2. Section of adenoma showing oedematous adenomatous tissue, focal calcification (arrow) and organizing thrombus in a vessel (arrowhead). Haematoxylin and eosin × 100.

orrhage into a parathyroid cyst. A serum sample obtained at 16 weeks gestation for AFP was retrieved, and found to be suggestive of primary hyperparathyroidism (calcium: 2·91 mmol/l, phosphates: 0·57 mmol/l, albumin: 39 g/l, urea: 3·7 mmol/l). However, due to lack of specific symptoms and as pregnancy gives some protection against hypercalcaemia, because of the hypoalbuminaemia and loss of calcium to the fetus (de Swiet 1984; Whally 1963), the condition progressed unnoticed until the development of postpartum hyperparathyroid crisis. Lehr & Krukowski (1961) showed in rats that advanced pregnancy provided remarkable protection against the toxic sequelae of parathyroid hormone overdosage but this protection did not extend into the immediate postpartum period. It would seem that hyperparathyroid crisis is more likely to occur in the immediate postpartum period than antenatally. The development of antenatal hyperparathyroid crisis as reported by Whalley (1963) may be associated with fetal death which could augment maternal hypercalcaemia since a significant amount of calcium is removed daily from the maternal circulation by the fetus (Whalley 1963).

It should be stressed that the definitive treatment is immediate surgical removal of the abnormal parathyroid tissue in both fetal and maternal interests. A review by Wilson *et al.* (1983) revealed a 26% pregnancy loss (abortion, stillbirth or neonatal death) and a 33% frequency of neonatal calcium disturbance in 61 patients not operated upon compared with 6% and 0% respectively in 16 women who had a parathyroidectomy during pregnancy. The unfavourable outcome in our patient was not only because of the severity of the condition at presentation but also as it was compounded with irreversible renal damage, acute pancreatitis and respiratory distress syndrome. We would agree with Thomason *et al.* (1981), that pregnant women with both hyperparathyroidism and pancreatitis are at grave risk especially when hyperparathyroid crisis occurs. As noted previously (Whalley 1963), in our patient also the baby was normal in all respects. However, hypocalcaemic tetany is a common neonatal complication which may provide the initial diagnostic clue to the maternal disease (Pitkin 1985).

We conclude by emphasizing the importance of the need of more thorough investigations of patients with non-specific symptoms during pregnancy. Pregnant women with excessive fatigue, weakness, vomiting, aching bones, or with history of renal calculi, peptic ulcer, acute pancreatitis and those with history of unexplained stillbirth should have serum biochemistry as a screening test. It is worth noting that the total serum calcium is depressed during pregnancy because of physiological hypoalbuminaemia but free calcium is unchanged and that total serum calcium normally falls as gestation progresses (Thomason *et al.* 1981).

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Received 4 September 1986
Accepted 20 November 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol 94, pp. 811-812

'Placental abruption' with disseminated intravascular coagulopathy in the second trimester of pregnancy with fetal survival. Case report

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Case report

A 25-year-old healthy white woman, who had had one previous normal pregnancy and who had already received antenatal care presented at 18 weeks gestation with acute and intense low abdominal pain, sudden severe bleeding from the gums and spontaneous ecchymoses. No trauma was reported. The blood pressure was 140/100 mmHg, the pulse 92 and fetal heart movements were detected. The cervix was formed and undilated and there was no blood in the vagina. Uterine size was compatible with the gestational age. There was abnormal bruising at the venepuncture sites. A few hours later slight vaginal blood loss was observed.

The laboratory confirmed a severe consumptive coagulopathy with a prolonged partial thromboplastin time, decreased plasma fibrinogen and platelet count and increased serum fibrin degradation products.

An ultrasound examination showed a single live fetus with a biparietal diameter compatible with 18 weeks gestation, a normal amniotic fluid volume and a grade '0' posterior placenta. No retroplacental haematoma was seen on that occasion.

Packed red cells and fresh frozen plasma was the immediate treatment; 24 h after admission there was no bleeding, vital signs and functions were within the normal range and the fetal heart sounds were still present. On the 5th day the coagulation system had returned to normal and an ultrasound scan showed a 40 × 50 mm hypoechoid area between the uterine wall and the placenta with the fetus still alive. On the 10th day the ultrasound findings were very much the same.

The patient was discharged on the 24th day and followed in the antenatal clinic. Another ultrasound observation at 30 weeks failed to identify any abnormality and there was a complete absence of the retroplacental abnormality.

At 33 weeks the patient was admitted because of premature rupture of the membranes. A week later spontaneous labour began and she was delivered vaginally of a live and normal female baby with a birthweight of 2000 g and Apgar scores of 9 and 10 at 1 and 5 min.

On the maternal side of the placenta there was a flattened yellowish 60 × 40 mm area with the microscopic characteristics of an ischaemic necrotic infarction.

Mother and daughter were discharged on the 10th day after birth, both doing well.

Discussion

Pathologic modifications of the coagulation system are important causes of maternal and fetal morbidity and mortality and can occur at any time during the pregnancy as a consequence of certain obstetric complications or as a specific defect of the coagulation systems (Hibbard & Jeffcoate 1966). Disseminated intravascular coagulopathy (DIC) is more often seen in the third trimester of gestation and severe pre-eclampsia, eclampsia, placental abruption, amniotic fluid embolism, heavy haemorrhage, prolonged retention of a dead fetus, induced abortion and sepsis are associated factors (Pritchard *et al.* 1985). Maternal recovery is the rule

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with prompt and adequate treatment but fetal death is common. Expeditious delivery (vaginally if possible) is usually recommended (Knab 1978) and this halts the consumptive coagulopathy (Sher & Statland 1985).

The retroplacental haematoma in the premature separation of a normally implanted placenta is usually seen in the ultrasound scan only a few days after it actually happens (Macgahan *et al.* 1982), as the present case confirms.

Our patient had severe DIC in the second trimester following the partial separation of a normally implanted placenta and was managed conservatively. The DIC was controlled and the pregnancy continued to a successful conclusion.

Apparently placental abruption, even when complicated by DIC, can be self-limiting and there is clearly a place for cautious conservative management if the fetus is alive but obviously immature.

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Received 17 October 1986
Accepted 22 December 1986

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 813–814

SHORT COMMUNICATIONS

In utero meconium aspiration: an unpreventable cause of neonatal death

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A 28-year-old primigravida with an uncomplicated antenatal course presented in labour 5 days beyond term. Membranes were ruptured artificially revealing thick meconium stained amniotic fluid, but subsequent internal cardiography was normal apart from two late decelerations in the second stage. A live male infant was born by Neville-Barnes forceps for poor progress in the second stage of labour. At birth the baby gasped and cried; laryngoscopy was performed and no meconium was seen or aspirated from below the vocal cords. Despite 100% oxygen given by facial mask and then by endotracheal tube, the baby became cyanotic and bradycardic. The lungs were noted to be stiff when ventilated. Full cardiopulmonary resuscitation was performed after pneumothorax was excluded. In the course of resuscitation nalorphine, fresh frozen plasma, intravenous and intracardiac adrenaline were given to no effect. The baby died at 1 h of age. Apgar scores were given as 6 at 1 min and 2 at 5 min. At autopsy no congenital abnormalities were found and no meconium plugs were seen, but there was deep meconium aspiration with most alveoli lined with meconium (Fig. 1).

Discussion

The cause of death was deep meconium aspiration preventing adequate gas transfer across

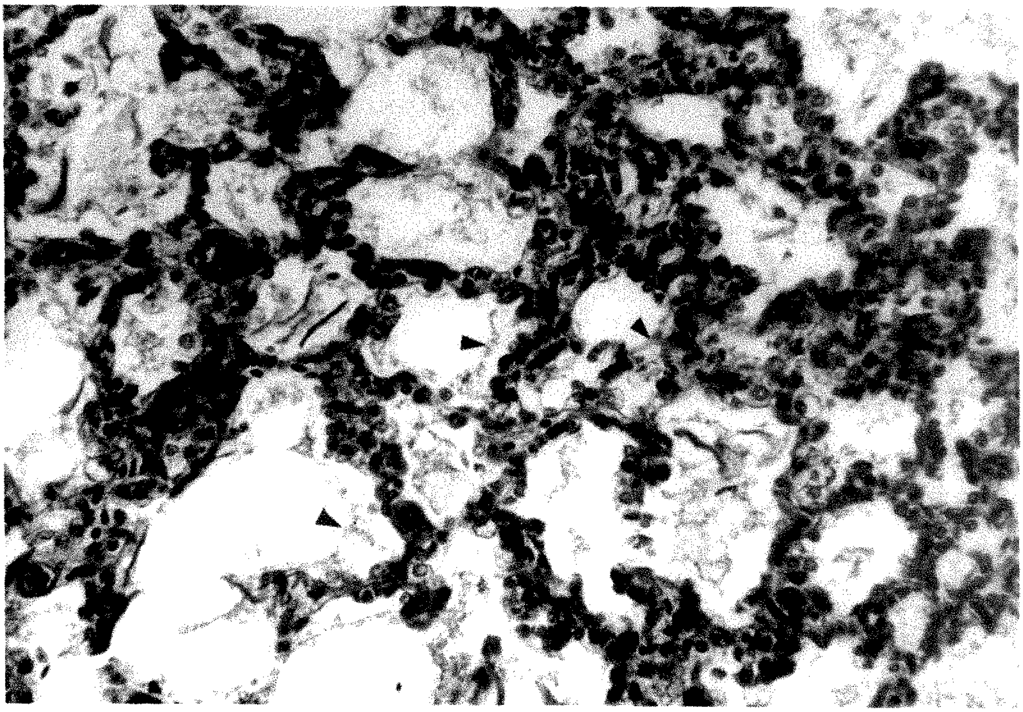

Fig. 1. Photomicrograph of lung showing aspirated meconium in pale grey. Arrowheads indicate adherence of meconium to alveolar walls (Attwood's stain × 275).

the alveoli. This degree of aspiration occurs *in utero* and is due to the hypoxic fetus gasping when there is already meconium in the amniotic fluid (Manning *et al.* 1978*a*).

In normal fetal breathing the net flow of fluid is out of the lungs due to both the production of fluid from the lungs and also the longer expiratory component of fetal chest movement. In the normal situation the aspiration of meconium is unlikely but if this balance is upset then aspiration can occur. Hypoxia has been demonstrated in animals to cause fetal gasping altering the direction of flow and allowing meconium to be aspirated (Manning *et al.* 1978*b*). The situation is worsened by fetal acidosis since this causes pulmonary vasoconstriction which results in decreased production of lung fluid (Davis *et al.* 1985; Manning *et al.* 1978*b*). Thus the infant is born with an unpredictable amount of damage done and intensive paediatric management will not affect the outcome (Davis *et al.* 1985). Associations have been found between abnormal fetal heart rate patterns in labour and meconium aspiration but these are not specific predictors (Dooley *et al.* 1985; Miller *et al.* 1975).

In some infants there can be associated pulmonary hypertension causing shunting of blood away from the lungs further impairing gas transfer (Murphy *et al.* 1981; Tyler *et al.* 1978).

At present, until the mechanisms are better understood, fetal meconium aspiration *in utero* will remain an unpreventable cause of neonatal death. It is recommended that fetal blood sampling be performed in all cases of thick meconium staining of amniotic fluid associated with abnormal fetal heart rate patterns in labour. Early delivery may possibly minimize the damage done *in utero*. In infants with persistent pulmonary hypertension at birth, Tolazoline may be given to reverse shunting and improve oxygenation.

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Received 3 December 1986
Accepted 26 February 1987

British Journal of Obstetrics and Gynaecology
August 1987, Vol 94, pp. 815–827

CORRESPONDENCE

Langerhans' cell density in the normal exocervical epithelium and in the cervical intraepithelial neoplasia

Dear Sir,

We feel that several of the observations made by Caorsi & Figueroa [*Br J Obstet Gynaecol* (1986) **93,** 993–998] need challenging. We have also studied Langerhans' cells in intraepithelial neoplasia, invasive carcinoma, and in the normal cervix, using a variety of methods including ATPase, S-100, anti-T-6 antibody and electron microscopy. Our initial observations of these cells were in healing cervical epithelium after laser treatment (MacLean 1984).

Caorsi & Figueroa state that material was obtained from cervices with early invasive carcinoma, and thereafter give information relating to cervical intraepithelial neoplasia (CIN). By using epithelial sheets separated from underlying stroma, it is not possible to know whether they are in fact examining sheets of CIN or sheets of neoplastic epithelium overlying early stromal invasion. Further, the authors make no mention of the practical difficulties encountered by the technique of EDTA separation of cervical epithelium from underlying stroma. Epidermidization of the cervical crypts makes separation more difficult and renders counting of the Langerhans' cells in sheets from these areas virtually impossible. Moreover, these crypts occur in the transformation zone, the very area affected by the neoplastic change.

Unfortunately the authors did not report the numbers of Langerhans' cells seen per 100 basal cells or per linear millimetre in the routinely sectioned epithelium, even though they used such sections from the epithelial sheets for the diagnosis of CIN.

There are no prints of zinc-iodide-osmium (ZIO) stained normal or abnormal sheets in the article. This would have been of great benefit as the numbers of Langerhans' cells seen by us, even in normal epithelial sheets using an ATPase technique, vastly exceed those reported in the publication The mean number of Langerhans' cells that we identified is 629/mm^2 (SE30) in the normal transformation zone and 595/mm^2 (SE19) in normal ectocervix compared with 10·4 in the article. Reported values for normal skin are 460–1000 Langerhans' cells/mm^2 (Rowden 1981).

Using a 'linear' measurement for quantitation of Langerhans' cells and an anti T-6 monoclonal antibody (NA 1/34, SERA LAB) on frozen sections of normal skin, Ashworth *et al* (1986) showed the Langerhans' cell density to be 31 per 200 basal cells Our results using the same technique show the normal cervix to have a mean of 7·96 Langerhans' cells per 100 basal cells in the transformation zone (SE 0·62) and a mean of 8·2 per 100 basal cells in the ectocervix (SE 0·65). From our results using different methods for staining and counting Langerhans' cells, it appears that cervix contains 50–60% of Langerhans' cells of skin and not 1% as reported by the authors in their study. This 50–60 times difference is difficult to explain, except perhaps that zinc-iodide-osmium is an insensitive, though allegedly specific, technique for Langerhans' cell demonstration in the cervix (Figueroa & Caorsi 1980).

The significance of the change in Langerhans' cell morphology seen with ZIO staining in neoplastic cervical epithelium is purely speculative, as ZIO staining has not been shown to have any functional relevance. Our observations do confirm that Langerhans' cell morphology appears changed following staining of neoplastic cervical epithelium with ATPase and anti-T-6 antibody. Using monoclonal antibodies against functional markers (HLA DR antigens) of Langerhans' cells shows their presence frequently also on the dysplastic epithelial cells themselves. This often obscures the Langerhans' cells which require these cell surface antigens for antigen presentation and T-cell recognition. These HLA DR positive keratinocytes have been confirmed by others (Morris *et al.* 1983), and may contribute more than previously appreciated to the local immune response in abnormal cervical epithelium. They certainly complicate the interpretation of functional Langerhans' cells in neoplastic cervical epithelium.

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Authors' reply

Dear Sir,

In reply to the letter by Hawthorn & McLean which challenges some of our findings we would like to make the following comments. The main objectives of our paper were: (i) to confirm, using different methods, the increase in Langerhans' cell density in cervical intraepithelial neoplasia (CIN) which we had reported previously (Caorsi & Figueroa 1984); (ii) to establish whether there is some correlation between Langerhans' cell density and the different degrees of CIN.

The results did show an increase in Langerhans' cell density in CIN as compared with the normal exocervix and that the magnitude of such an increase and the degree of severity of the neoplastic changes are closely related phenomena.

To estimate the Langerhans' cell density we used epithelial sheets stained in a block with ZIO. Since, with this method the entire profile of each Langerhans' cell can be seen, it is obviously more reliable than one based on tissue sections. In our hands, the use of EDTA to obtain epithelial sheets from the exocervix has given excellent results. Furthermore, we found that in the neoplastic exocervix it was easier to obtain the laminae; this was shown by the fact that the incubation time in EDTA required for the detachment of the epithelial layer was shorter in the neoplastic exocervix than in samples from normal exocervices. We agree with Hawthorn & McLean that when separating the laminae from the transformation zone we only obtain the surface epithelium and not that of the cervical crypts undergoing epidermidization. We were aware of this fact and believed, and still believe, it does not weaken our results and conclusions for the following reasons: (i) we looked for a *correlation* between Langerhans' cell density and CIN grades rather than for absolute values, and found such a correlation in the surface epithelium obtained as epithelial laminae; (ii) the CIN grade was established in microtome sections of the same epithelial sheets which had been used previously to estimate Langerhans' cell density; (iii) there seems to be no difference between the Langerhans' cell density in the crypts and that of the surface for a given CIN grade (Caorsi & Figueroa 1984).

Another objection to our paper is that we made no mention of the number of Langerhans' cells in the sectioned epithelium. As the Langerhans' cells were counted in the epithelial laminae which *afterwards* were embedded and sectioned, we see no need to repeat the counting. It must be stressed that the laminae were used to establish, in a reliable way, Langerhan's cell density, and the sections of the *same* laminae were used for the diagnosis of CIN.

With respect to the discrepancy concerning Langerhans' cell density in the exocervix, we think it should be ascribed to sampling problems and not to the method used to demonstrate the Langerhans' cells. This assumption is based on the following facts: (i) Epithelial sheets from both normal and neoplastic exocervices stained with ZIO show that the Langerhans' cells are irregularly distributed throughout the exocervix, with some areas displaying a high density

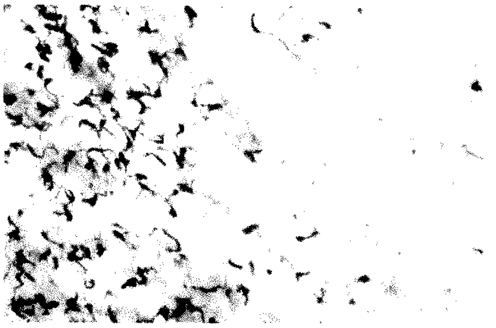

Fig. 1. A portion of an epithelial sheet showing the uneven distribution of Langerhans' cells in the exocervical epithelium (ZIO staining)×80.

and others virtually devoid of these cells (Fig. 1). In a previous paper we reported that in small areas, especially in the transformation zone, the Langerhans' cell density could reach a mean of 178·5 (SD 18·6) cells/mm² in normal cervices and 645·1 (22) cells/mm² in neoplastic cervices (Caorsi & Figueroa 1984). (ii) When counting Langerhans' cells we examined the entire exocervix and not just small biopsy samples. (iii) By using antibodies against S-100 protein (Fig. 2) and OK-T6 we have also observed an uneven distribution of Langerhans' cells in invasive prongs of exocervical squamous carcinoma. (iv) We have found no differences in Langerhans' cell density in the epidermis using the ZIO method or immunoperoxidase method for S-100 protein. Therefore, the former method should be regarded as being as sensitive as the latter to demonstrate Langerhans' cells. (v) McArdle & Muller (1986) using exocervical biopsies and immunocytochemistry for S-100 protein, that is material and methods similar to those reportedly used by Hawthorn & MacLean, have reported Langerhans' cell density in the normal exocervix of 12·6 cells/mm² and in CIN of 45·0 cells/mm², quite similar to those reported by us.

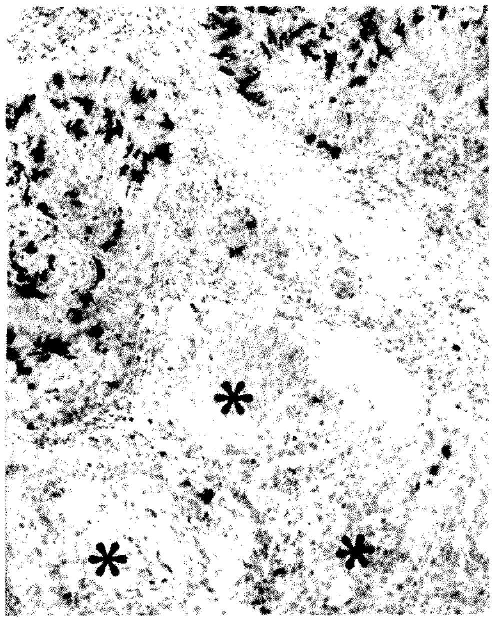

Fig. 2. A similarly uneven distribution of Langerhans' cells is observed in invasive prongs when an antibody against S-100 protein is used (dilution 1:8000). Asterisks show invasive prongs devoid of Langerhans' cells (peroxidase-anti-peroxidase method counterstained with haematoxylin)×180.

Finally, while we accept that the functional relevance of ZIO staining is at present unknown, the method we use selectively stains the Langerhans' cell granule (Rodriguez & Caorsi 1978; Figueroa & Caorsi 1980), and the Langerhans' cell granule has widely been regarded as the Langerhans' cell marker. Only when the functional role of the Langerhans' cell granule is established will we be in a position to know the significance of the ZIO staining of the Langerhans' cell. The same criticism could be made of the ATPase reaction and the immunostaining for S-100 protein, since at present no functional meaning can be envisaged for these two reactions in Langerhans' cells, and although selective, they are not specific methods for Langerhans' cells. It is obvious that as more and different methods are used to study Langerhans' cells the more reliable and meaningful the results are. In this respect we agree with the approach of Hawthorn & McLean and for this reason we have incorporated in our research immunocytochemistry at the light and electron microscopic level, using antibodies against S-100 protein and OK-T6.

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Blood group antibody screening tests during pregnancy

Dear Sir,

Bowell and colleagues [*Br J Obstet Gynaecol* (1986) **93,** 1038–1043] recommended the following blood sampling routine in pregnancy: all women should be screened for blood group antibodies early in pregnancy and retested at about 34–36 weeks gestation. In addition all women who are either rhesus (D) positive or who have been previously transfused should be rechecked at 28 weeks gestation.

Like Hardy & Napier (1981), Bowell *et al.* (1986) found that in a considerable proportion of sensitized pregnant women previous transfusion(s) could be responsible for the blood group antibody.

Another factor may, however, be equally important since in a survey covering the period 1.1.1980–31.12.1983 we found that 9 out of 18 immunized nulliparae gave a history of one or more spontaneous or induced abortions (Reiche & Georgsen 1986). This is significantly different from the observed frequency of abortions (15%) among 1449 non-immunized nulliparae, which was found in the same region by Lylloff *et al.* (1986) (χ^2-test: $P<10^{-4}$).

Transplacental haemorrhage which seems to be prerequisite for immunizations to occur was described in patients with spontaneous and induced abortions by Matthews & Matthews (1969).

In 1973 abortion was legalized in Denmark and it was in the 1970s most often performed in women aged between 15 and 25. In 1980–1983 these women were between 25 and 30 and thus in their most fertile period. In 1980 there were 51 087 live births and 20 791 legal abortions in Denmark (Denmark's statistics 1985). Of the induced abortions 44% were performed in nulliparae (Danish National Health Service 1984).

Our data thus indicate that induced abortion is another important factor for development of erythrocyte antibodies in the fertile women and this factor may well be as important as previous transfusion therapy and deliveries.

In a few cases this will eventually lead to haemolytic disease of the newborn, mostly in mild forms, but as pointed out by Bowell *et al.* (1986), it will always be of concern in selecting compatible blood for transfusion for the mothers.

On the basis of these findings it seems reasonable that screening for blood group antibodies at 28 weeks gestation should include not only previously transfused women, but also all women with previous abortions.

Finally the risk of immunization due to induced abortion should also be considered when advising women about contraception.

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Authors' reply

Dear Sir,

Although we did not specifically examine the influence of abortion on allo-immunization, we would certainly agree with Georgsen and colleagues that both spontaneous and therapeutic abortions are recognized risk factors for immunization. This point is amply demonstrated by the occurrence of Rhesus (D) immunization following abortion, hence the now widely accepted need for prophylaxis at this time. However, we would question whether all post-abortion patients would require an additional screen for antibodies (at 28 weeks gestation) in subsequent pregnancies.

Although there are exceptions, notably due to the so-called hyper-responders, in general we believe that the rate of immunization is principally dependent upon the size of dose of antigen given. Hence immunization probably occurs more frequently after blood transfusion than at parturition, and even less often following abortion. Feto-maternal haemorrhages after abortion are known to be comparatively small especially within the first trimester (Gjode *et al.* 1982), may possibly reflect the nature and procedure used (Keith & Berger 1982), and require smaller doses of anti-Rhesus (D) prophylaxis than at parturition (WHO 1971). To treat all post-abortion cases in a similar manner therefore would seem to be both inappropriate and wasteful of resources, the more so when probably fewer women become immunized then than at parturition. Furthermore, compared to Rhesus (D) most other blood group antigens are rather poor immunogens (Mollison 1983), probably requiring either a larger dose and/or more frequent exposure to antigen to initiate antibody production.

On the other hand, because of a 10-fold increased risk of immunization in previously transfused patients, and on account of the severe clinical consequences of Rhesus (D) sensitization, we feel that there is clear justification for an intermediate (28 week) test for both these higher risk groups. Other than for the post-abortion cases that come into either of these categories, we doubt whether for the remainder the risk of immunization and the clinical consequences of such an event would draw favourable comparison. In any case we believe that the majority of post-abortion allo-immunizations should be recognized in the initial test during the following pregnancy and virtually all would be detected at the time of the 34/36 week sample.

Our recommended protocol represents a compromise between the ideal and the practicable. There are indeed several ways, additional post-abortion testing included, in which it might be improved, but at much extra cost and for relatively little return. We conclude therefore, that for all post-abortion patients a routine 28 week assay during the next pregnancy would not be justifiable during these frugal times.

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The value of CA 125 serum assay in the management of ovarian cancer. Commentary

Dear Sir,

Whilst agreeing with Joanna Lambert's conclusions [*Br J Obstet Gynaecol* (1987) **94,** 193–195] in relation to monitoring established ovarian cancer, which has been extensively studied, we felt it was regrettable that she reached such firm conclusions on the potential of CA 125 for early diagnosis. Little data exist on this subject and her statement that CA 125 has no place in screening asymptomatic women for epithelial ovarian carcinoma is premature, if not wrong, for the following reasons:

1. Normal upper limit. The upper limit of 35 U/ml used in most studies of monitoring established ovarian cancer was arbitrarily defined by Bast *et al.* (1983) on the basis of serum levels in male and female blood donors of median age 34 years. The normal range of serum levels for postmenopausal women has not yet been established; 35 U/ml may be inappropriate for a screening programme which aims to achieve high sensitivity in postmenopausal women at risk. Preliminary results from the first 1010 apparently healthy postmenopausal women (mean age 54·2 years, range 45–75 years) studied at The London Hospital indicate that the 90th, 95th and 98th centiles for serum CA 125 in these women are 23·2 U/ml, 26·3 U/ml and 30·85 U/ml, respectively.
2. Specificity. It is not necessary for a serum test for early ovarian cancer to be 100% specific. Ultrasound scanning is an extremely good method of imaging the postmenopausal ovary (Campbell *et al.* 1982) and a suitable second line screening test (cf. cervical cytology and colposcopy). It may be appropriate to sacrifice a degree of specificity in order to increase the sensitivity for early stage disease. Furthermore many of the non-malignant causes of an elevated CA 125 level do not occur in postmenopausal women who would be the target of a screening programme (e.g. endometriosis, pregnancy, pelvic inflammatory disease).
3. Sensitivity. Dr Lambert emphasized the need for a critical tumour mass to cause elevated serum CA 125 levels, referring in particular to 11 patients with persistent disease nodules less than 1 cm diameter at second look surgery who had CA 125 levels less than 35 U/ml (Canney *et al.* 1984). As clinically diagnosed stage I ovarian malignancies are rarely less than 5 cm diameter at presentation, critical mass is unlikely to be the cause of low serum levels of CA 125 in these women. Preoperative serum CA 125 levels in stage I and II disease have not been reported in a large series of cases or in relation to an appropriate upper limit of normal for screening postmenopausal women.

CA 125 may not be the ultimate answer to the quest for early diagnosis of ovarian cancer but it would be foolish to dismiss this possibility before the relevant information is available.

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Authors' reply

Dear Sir,

Effective screening for occult ovarian cancer requires tests that are both sensitive and specific.

Data so far suggest that CA 125 is elevated in most patients with ovarian cancer. As a single test, however, CA 125 is not sufficiently specific to permit cost effective screening of an apparently healthy population. Drs Jacobs and Oram report on their preliminary results from 1010 apparently healthy postmenopausal women, indicating that in order to achieve maximal sensitivity, the upper normal limit for serum CA 125 should be set at 23 units/ml. This is probably a very valid suggestion, but more data are still required. Although ultrasound scanning is an extremely good method of imaging the postmenopausal ovary, its place as a screening test has not been fully established, nor whether it offers any significant advantages over vaginal examination.

The lack of specificity and sensitivity using a single marker such as CA 125 may be improved by using serum markers in combination, but prospective studies are required to test this. I agree with Dr Jacobs and Dr Oram that a specific tumour marker for epithelial ovarian carcinoma is highly desirable, both as a screening test, and in monitoring patients who are apparently in clinical remission, but I will still stick to my earlier conclusion that CA 125 on its own has no place in screening asymptomatic women for epithelial ovarian carcinoma. Its value, together with other tumour markers and with other diagnostic approaches, should be assessed in properly conducted trials.

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The relation of birthweight to histological appearances in vessels of the placental bed

Dear Sir,
McFadyen *et al.* [*Br J Obstet Gynaecol* (1986) **93**, 476–481] found a significantly lower birthweight in the babies born to mothers with atherosis than in those with other placental bed histology. Hypertension also occurred most frequently in those women who had atherosis in the placental bed. Maternal hypertension and a lower birthweight in the babies were also observed in cases with absence of the normal physiological changes of pregnancy. Interestingly, the authors pointed out the marked reduction in birthweight associated with atherosis, greater than in those whose vessels show only inadequate physiological changes.

The authors stated that examination of the vessels attached to the chorionic membranes did not add any useful information. Robertson *et al.* (1986) mentioned that 'the best material to use to identify acute atherosis is the decidua vera or parietalis and not the placental bed or the basal plate of the placenta. The decidua vera obviously is devoid of migratory trophoblast and its associated effects on maternal tissues, including spiral arteries. The vasculopathy is therefore seen in the decidua vera in its 'pure' form, uncomplicated by pre-existing trophoblast-induced vascular changes. Thus, in studies concerned mainly with vasculopathies, it is good practice to take biopsy specimens of the decidua parietalis in addition to those from the placental bed. Rolled-up strips of the placental membranes are a valuable additional source of decidua vera containing portions of decidual spiral arteries, which may show acute atherosis. Difficulties in interpretation of pathologic lesions arise in the uteroplacental arteries themselves. In their decidual segments the vessels have been altered almost beyond recognition through involvement with endovascular trophoblast and it becomes very difficult to differentiate the characteristic fibrinoid material in the vessel wall from the fibrinoid necrosis of an acute vasculopathy. Furthermore, sensescent cells in the physiologic changes, including trophoblast, accumulate lipid in their cytoplasm'.

We found absence of physiological changes in basal plate associated with acute atherosis in basal plate and/or parietal decidua in cases with idiopathic intrauterine growth retardation and in those with pre-eclampsia with or without intrauterine growth retardation (Althabe *et al.* 1985; Labarrere & Althabe 1985). Acute atherosis was described in idiopathic intrauterine growth retardation, pre-eclampsia with or without intrauterine growth retardation, insulin-dependent diabetes, sustained chronic hypertension with or without superimposed pre-eclampsia, first-trimester abortions and also in some autoimmune diseases (Robertson *et al.* 1981; Sheppard & Bonnar 1981; Kitzmiller *et al.* 1981; Althabe *et al.* 1985; Labarrere & Althabe 1985; Lichtig *et al.* 1985; Labarrere *et al* 1986). Similar vascular lesions were described in rejected renal, cardiac and hepatic transplants (Dempster *et al.* 1964; Hess *et al.* 1983; Demetris *et al.* 1985).

A possible immunological origin of atherosis is suggested by the finding of immunoglobulins and complement in the walls of damaged placental vessels (Laberrere *et al.* 1985). A maternal immunological aggression against placental tissues may cause a deficit in placentation, which may be related to the maternal vasculopathies described elsewhere. Low birthweight may be related to placental and fetal ischaemia secondary to a high extension and severity of maternal vascular lesions in the placenta. The hypertension of pregnancy may be a compensatory mechanism to ensure an adequate blood supply to the placenta when the physiological changes fail to occur and then may exert a beneficial influence on the development of the fetus (Gerretsen *et al.* 1981). When this compensatory mechanism is either insufficient or does not appear, the inadequate blood supply will be rather related to a fetal growth retardation of variable severity (Gerretsen *et al.* 1981). It may be very interesting to know whether the lesions of acute atherosis described in the present paper have deposits of immunoglobulins and complement in the walls supporting the possibility of an immune-mediated mechanism in their aetiology.

On the other hand, lesions of chronic villitis of unknown aetiology in the placenta have been described associated with intrauterine growth retardation, pre-eclampsia with or without intrauterine growth retardation, sustained chronic hypertension with superimposed pre-eclampsia and some autoimmune diseases (Labarrere & Althabe 1985, 1986; Labarrere *et al.* 1986). These lesions have been proposed as another expression of a maternal immunological aggression against placental tissues. It would be very interesting to know the incidence and severity of chronic villitis in the placentae studied by McFadyen *et al.* (1986), and their relationship with intrauterine growth retardation and maternal hypertension during pregnancy.

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The short-term effect of radical hysterectomy on urethral and bladder function

Dear Sir,

We should like to congratulate Farquharson *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 351–357] on their excellent article in which they report urodynamic changes after radical hysterectomy. The authors state that the aetiology of postoperative genuine stress incontinence remains an enigma but hint that pre-operative bladder neck incompetence may be a risk factor, though they did not give a clear explanation for this.

We may have such an explanation and this stems from work on a much larger series of patients. In a study of 98 women proven to be continent on pad testing (Versi & Cardozo 1986) and videocystourethrography (Bates *et al.* 1970), we noted that 50% of them had an incompetent bladder neck on coughing (Versi *et al.* 1986). Analysis of urethral pressure profile transmission pressure ratios (Hilton & Stanton 1983) revealed that women with an incompetent bladder neck remained continent by augmenting their distal transmission pressure ratios and so maintained their urethral stress profile length (Versi *et al.* 1984*a*).

This suggests that women with bladder neck funnelling (beaking) on coughing use their distal sphincter mechanisms. These mechanisms can be reinforced by voluntary contraction of the peri-urethral sphincter (Griffiths 1980) and also possibly the pelvic floor. Such an augmentation would require an intact neural input and so we postulate that radical surgery may interfere with this.

Analysis of transmission pressure ratios in women with an incompetent bladder neck shows that the zone of maximum pressure transmission is more distal than in women with a competent bladder neck. In other words, the most important part of their urethra that maintains continence is more distally located. This could explain why some women are incontinent after radical vulvectomy when the distal urethra is excised and perhaps pre-operative urethral pressure profilometry could be used to predict this (Versi *et al.* 1984*b*).

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Idiopathic acute fatty liver of pregnancy associated with transient diabetes insipidus. Case report

Dr Cammu and colleagues reported a very well documented and interesting example of a patient with transient diabetes insipidus (DI) of pregnancy [*Br J Obstet Gynaecol* (1987) **94**, 173–178]. They suggested that their patient differed from those in the literature because she was able to concentrate her urine when treated with exogenous 'vasopressin' and the others did not. This conclusion may be incorrect; they administered the analogue desamino-cys^1-D-Arg^8-vasopressin (dDAVP) and not arginine vasopressin (AVP). The use of the former preparation may be critically important in these cases.

We described three women with transient DI of pregnancy who were resistant to large doses of pitressin (Barron *et al.* 1984). All recovered during the puerperium. One patient had measurable immunoreactive AVP far below levels expected for her degree of hypertonicity while her vasopressinase levels were surprisingly high when measured postpartum. Unfortunately we had insufficient sample to determine bioactivity. We therefore cautiously labelled our patients as having transient 'vasopressin resistant' not 'nephrogenic' DI.

We subsequently became aware that dDAVP is quite resistant to the cystine aminopeptidase which inactivates AVP and waited for the next example of this rare syndrome. We have not, however, had the opportunity to treat one, but a former colleage, Dr J A. Durr in Denver, has studied such a case (Durr *et al.* 1985). The patient was resistant to industrial doses of AVP but concentrated her urine rapidly with dDAVP; her vasopressinase levels postpartum were 4–6 fold greater than those expected near term, and the authors convincingly demonstrated that the circulating immunoreactive AVP (half an hour after 30 u of aqueous pitressin), which measured over 200 pg/ml, was not biologically reactive and probably represented fragments. The situation, however, is more complicated as Ford & Lumpkin (1986) have recently described a patient resistant to both AVP and dDAVP.

Finally let us make two comments. Vasopressinase may circulate for 4–6 weeks after delivery (unpublished observations) and the metabolic clearance of AVP near term is 4-fold that in non-pregnant populations (Davison *et al.* 1987), making all pregnant women susceptible to polyuric states.

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Authors' reply

We thank Drs Lindheimer, Barron and Davison for the insight they provide into the interpretation of the apparently contradictory findings: on one hand the high levels of circulating vasopressin (AVP), making 'central' DI in the sense of post-pituitary insufficiency unlikely, and on the other hand the response of the kidneys to desamino-cys^1-D-Arg^8-vasopressin (dDAVP), making 'nephrogenic' DI in the sense of unresponsiveness of the kidney to vasopressin unlikely. Probably, the exact interpretation is indeed that the endogeneously secreted vasopressin (AVP) loses its bioactivity at the level of the renal receptors. This may be due to increased breakdown or stereostatic changes in the vasopressin (AVP) molecule or to changes in responsiveness of the renal receptors to AVP but not to dDAVP. The data provided by Drs Lindheimer, Barron and Davison may point to the former mechanism.

However, the conclusion from our observations remains valid: the polyuric state seen in our patient was demonstrated not to be of central origin in that neither functional nor morphological abnormalities were present at the level of the posterior pituitary gland. Hence, the label 'nephrogenic' diabetes insipidus was chosen to express the non-central origin. But in view of recent data about the relative resistance of dDAVP to vasopressinase (Durr *et al.* 1985), the label 'non-central' would have been more appropriate. Finally, our case illustrates that polyuric states (even of transient character) can be efficiently managed by administration of dDAVP.

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Screening for light-for-gestational age infants: a comparison of three simple measurements

Dear Sir,

Mathai *et al.* [*Br J Obstet Gynaecol* (1987) **94**, 217–221] imply that the sensitivity of diagnosing intrauterine growth retardation (IUGR) by serial symphysis-fundal height measurements was better than that of Rosenberg *et al.* (1982). This is not so; when the high risk and low risk cases are pooled, the sensitivity in Mathai's study (47/59) is no different from that reported by Rosenberg *et al.* (1982) (32/48; $\chi^2 = 2{\cdot}313$, $0{\cdot}50 > P > 0{\cdot}10$).

There are two other criticisms of this study. Only 250 patients were used in the construction of the standard graph of fundal height, and the number of measurements to calculate the means and standard deviations of some gestational ages was very small (11 at 28 weeks, 14 at 29 weeks). Their standard values therefore may not represent the whole population. Secondly, the interpretation of the data in the study group is surprising. They specified that a fundal height value >1SD below the mean on one occasion was predictive of IUGR. One would expect therefore that 16% of their normally grown babies would have been wrongly predicted as having IUGR. The actual figure for the whole study was 44/299 (15%). In a small study such as this such a degree of concurrence with the theoretical figure is almost too good to be true. Furthermore, there would be a 16% chance *with each measurement* of a false positive diagnosis of IUGR; if in an average pregnancy five measurements were performed then it is surprising that the rate of false positive diagnosis was still only 15%. Rosenberg *et al.* (1982) required two consecutive or three isolated fundal height readings to be below the 10th centile to be predictive of IUGR. Even with these more stringent criteria, the specificity was lower (433/460 (69%)).

Mathai *et al.* (1987) make one important statement when they suggest that the technique used by Rosenberg *et al.* (1982) to measure the fundal height may have been faulty. This may be correct; in that study the question of inter-observer variation was not considered. The fundal heights were measured by a large number of midwives and junior doctors at three separate clinics. Although all personnel received training in the technique before the study started, yet because of the fragmented nature of the antenatal clinics and the rapid turnover of staff, it is possible that errors in measuring the fundal height may have occurred more frequently than was realized during the study. It is interesting that those publications reporting a high sensitivity of serial fundal height estimations in the diagnosis of IUGR have been small, with a small number of observers (Belizan *et al.* 1978; Quaranta *et al.* (1981), while the larger studies report much lower sensitivities (Persson *et al.* 1986). Since sensitivity and specificity are independent of the prevalence of IUGR in the population, these differences in sensitivity must be partly due to inter-observer variation. Persson *et al.* (1986) reported a series of 2919 patients spread out over three clinics, and a large number of personnel must have been employed in measuring the fundal heights. Although they were given 'oral and written instruction' on the technique, it must have been difficult to ensure quality control in such a large study, and this may account for the resulting low sensitivity (27%).

Another problem of previous studies has been the definition of IUGR, which is nearly always a birthweight below the 10th centile. Yet it is accepted that many babies below the 10th centile are symmetrically small and do not have perinatal problems; conversely some babies above the 10th centile have asymmetrical IUGR. The whole purpose of serial fundal height measurements is to detect asymmetrical growth retardation due to uteroplacental insufficiency; since these pregnancies often have oligohydramnios, it may be that fundal height measurements are more sensitive in diagnosing asymmetrical growth retardation than in detecting babies whose birthweights are below the 10th centile. This may partly explain why the sensitivity in small studies is greater than in large studies, since the small studies tend to concentrate on high risk patients, with a high proportion of cases with asymmetrical IUGR.

There have been several publications in the past 10 years on the diagnosis of IUGR by serial symphysis-fundal height measurements, and the results have been conflicting, for the reasons outlined above. The definitive study will involve a large number of patients, where the fundal height measurements are performed by a few trained observers whose inter-observer variation is known and is regularly tested throughout the study, and where the definition of IUGR, is some measurement of asymmetrical IUGR, such as the ponderal index, or the weight-length ratio (Persson *et al.* 1986). Such a study will be expensive in terms of funding and of time, but is urgently required to establish the role of fundal heights in the diagnosis of IUGR.

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Authors' reply

We agree that the number of measurements used to calculate the means and standard deviations at some early gestations are small and therefore standard values at these gestations may not represent the whole population. However, since most cases of intrauterine growth retardation (IUGR) are usually detectable only at or beyond 34 weeks gestation (after which there are larger numbers of measurements), these errors at earlier gestations are less likely to be of significance.

Standard graphs in our study were based on measurements on 250 consecutive women with low-risk pregnancies. The distribution of birthweight in this group was similar to that for our centre. The mean −1 SD at term in our centre is 2·436 kg and the 10th centile of birthweight at term is 2·336 kg. The cut-off level of mean −1 SD was selected to ensure satisfactory sensitivity and specificity. One would therefore expect that 16% of *all* babies in the study group with low-risk pregnancies would have been considered (correctly or incorrectly) to have IUGR. The actual number in the study was 47/208 (23%).

Consecutively low fundal height measurements are logically more reliable than single low measurements in the diagnosis of IUGR. However, since many women in our population fail to keep their appointment at the antenatal clinic, serial follow-up measurements are difficult if not impossible. Some of these women present far too late for help. We therefore considered even a single low fundal height measurement to be significant and that this was a more realistic assessment of the method in our situation.

Considerable inter-observer variation could occur in fundal height measurements. Common errors in measurements arise from varying degrees of flexion at the hips as well as from attempts to define the pubic symphysis through layers of clothing! The technique of measurement has to be standardized and there should be frequent quality control checks.

IUGR is a condition for which a screening programme is appropriate. A controlled trial should be carried out in which fundal height measurements form the initial screening method for IUGR, more sophisticated methods of diagnosis being used only in those pregnancies suspected to have IUGR by fundal height measurements. Such a study is indicated to confirm that good antepartum care does not necessarily depend on costly new technology but on simple techniques which are inexpensive, universally applicable and yet reliable.

Lastly, we are indeed surprised that Mr Grant has quoted his own data incorrectly (Rosenberg *et al.* 1982). The sensitivity using serial fundal height measurements alone in the diagnosis of IUGR in that study was 28/50 and not 32/48. This is significantly lower than the overall sensitivity in our study (47/59; $\chi^2 = 5{\cdot}99$, $P<0{\cdot}05$).

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Rosenberg, K., Grant, J. M., Tweedie, I., Aitchison, T. Gallager, F (1982) Measurements of fundal height as a screening test for fetal growth retardation *Br J Obstet Gynaecol* **89**, 447-450.

British Journal of Obstetrics and Gynaecology
August 1987, Vol. 94, pp. 828–832

BOOK REVIEWS

Strategies in Gynecologic Surgery (in the series Clinical Perspectives in Obstetrics and Gynecology) edited by H. J. Buchsbaum & L. A. Walton. Springer-Verlag, Berlin, 1986, 231 pages with figures and tables, DM 168

The Editors of this volume have called on 18 contributors, all save one from the USA. The chapter topics selected deal with those factors concerned with surgical outcome—i.e. the principles of surgical management. The book is well produced, fully indexed, and adequately referenced. In most chapters the references are not confined to American literature. Throughout the volume the wide experience and clinical wisdom of the contributing authors is apparent. There are numerous excellent illustrations, including line drawings, black and white photographs, etc., but in no sense does the book attempt to be a surgical atlas.

As one might expect in a contemporary American text, issues of 'informed consent' to operation attract quite extended consideration. There is an excellent section on suture materials and wound closure. The various abdominal incisions for gynaecological surgery are well described. Given the present vogue for transverse incisions it is well that we are reminded of three recent controlled trials comparing vertical and transverse incisions. These have shown that transverse incisions are not under less tension than vertical incisions and that there are similar rates of dehiscence with the two approaches.

I felt the author was rather ambivalent about the benefits of prophylactic intra-operative antibiotic cover for hysterectomy. In the control of intractable pelvic bleeding, David Gal advocates *proximal* ligation of the internal iliac artery 'to preserve pulsatile collateral aterial circulation'! My experience has been that more distal ligation of the arterial trunk is eminently satisfactory. Other minor criticisms are the omission of the great value of the sucker to locate and define the exact site of bleeding in deeper areas of the pelvic wound. In cases of vaginal agenesis only the McIndoe skin grafting technique is described and recommended, which would not accord with contemporary practice in this country.

Other topics dealt with include wound drainage, peri-operative thrombosis and embolism and intensive surgical care. The book is a useful addition to gynaecological surgical literature but, even with the pound riding high, few will be able to afford it!

Philip Myerscough

Active Management of Labour by Kieran O'Driscoll & Declan Meagher. Baillière Tindall, London, 1986, 204 pages with figures and tables, £9.95

The work of O'Driscoll and colleagues, incorporating ideas of Friedman and Philpott, is the baseline reference for the modern management of labour. The content of the second edition of this book is drawn from the original publications by the authors, starting with that on The Prevention of Prolonged Labour in 1969 up until the fetal heart monitoring trial in 1985. This is the Dublin gospel.

As one would expect, the second edition is little changed from the first except for the addition of sections on caesarean section rates, the cervix in labour and the monitoring trial. Dystocia leading to caesarean section and then repeat caesarean section as its sequel is unequivocally identified as the prime element in the epidemic of caesarean birth in many countries. The message is clear.

The early stages of labour are more easily understood when progressive effacement is added to changing cervical dilatation as discussed but this could be elaborated further in thinning of the effaced cervix and its application to the presenting part. Although the need for vaginal examination as opposed to rectal examination in early labour is accepted by the authors, the logic of persisting with routine rectal examination is difficult to appreciate, especially when information gained is less reliable. According to the authors, women preferred vaginal examination. It is perhaps surprising that the section on the role of the mother has not been expanded and it is here that our patients may differ. Not all women are happy about hourly rectal or vaginal examinations in early labour. Public relations are important in childbirth and the term 'acceleration' has been misunderstood by parents. We prefer to explain that the rate of labour progress is being restored to normal, rather than being speeded up. Consequently 'augmentation' is a better term.

The tenet that babies are better born by propulsion rather than traction cannot be stated often enough. The exhortation to use oxytocin for augmentation of second stage progress prior to, or instead of, forceps delivery is most apposite; clearly this is limited to delay in the second stage without evidence of fetal distress.

The forceful message and impressive statistics are striking, although more information about the significant number of babies dying in the labour ward would be interesting. The emphasis on augmentation of primigravid labour is important; nonetheless multigravid labour merits more consideration. Absolute rules are always disconcerting; this is evident in the description of drip rate, volume, duration of oxytocin dosage. As long as the human element remains central, control of oxytocin infusion by a simple peristaltic controller with dosage calculated in milliunits per minute deserves more than cursory dismissal. Indeed failure of the human element in controlling gravity fed oxytocin infusions has led to litigation. Why oxytocin augmentation should be forbidden in breech presentation when poor uterine action is at least as likely as in cephalic presentation remains a puzzle. The experience of others is that as long as the fetopelvic relation has been carefully assessed, careful treatment is reasonable and productive.

Nonetheless this book is a key reference for all those involved in labour ward care and should be on the shelf in all labour wards.

Donald Gibb

In Vitro Fertilization Norfolk edited by Howard W. Jones, Jr, Georgeanna Seagar Jones, Gary D. Hodgen & Zev Rosenwaks. Williams & Wilkins, Baltimore, 1986, 319 pages with figures and tables, £60.00

'Benefit from the Norfolk Experience—an inside look at the Jones Institute for Reproductive Medicine', or so the publisher's blurb goes, and I suppose for those who can't afford the fare to Virginia for the Fifth World IVF Congress, this book must be an acceptable alternative at £60. It is certainly a fascinating record of a remarkable achievement, the 21 chapters written by a total of 27 authors, all of them participants in the Norfolk IVF programme. The book is based on their experiences during 1981 through 1984 and covers all facets of management, including some aspects of physiology such as follicle and oocyte maturation. Inevitably in a book like this, there are good and not so good chapters. Much of the data is clear and interesting, while in a few cases it is anecdotal or indigestible. Four chapters on insemination and related topics are two or three too many. Inevitably much of the data and information is now available elsewhere, but there are nine detailed and informative appendices for those wanting to set up shop. All in all the book is a must for those working in the area, and most clinics and research units will probably want to have a copy for ease of reference. At £60 it is unlikely to attract the casual reader.

A. A. Templeton

Anesthesia in Obstetrics. Maternal, Fetal and Neonatal Aspects edited by G. A. Albright, J. E. Ferguson II, T. H. Joyce III & D. K. Stevenson. Butterworths, Boston & London, 1986, 622 pages with figures and tables, £65.00

This is the second edition of a book which was first published in 1978 and Dr Albright has assembled a team of co-authors from a variety of subspecialities to collaborate on 15 of the 21 chapters. The purpose of the book 'is to present a comprehensive, up-to-date, readable source of information on all aspects of obstetric anaesthesia . . . and to serve as a multi-disciplinary textbook and reference source for practitioners in anaesthesia, obstetrics and paediatrics and for nurses involved in the care of parturients and perinates'.

The book consists of six sections each being subdivided into several chapters. The first section is a good, concise, historical introduction with discussions on anaesthetic benefits and risks, maternal and perinatal mortality, pre-anaesthetic assessment and preparation, and it was reassuring to read that the practice of operator cum anaesthetist in the delivery room was condemned.

The second section deals with the physiology of pregnancy and labour together with descriptions of pelvimetry, use and types of forceps and the vacuum extractor. Although these descriptions are unusual in a textbook on obstetric anaesthesia, they might act as a reminder to anaesthetists but would certainly not be detailed enough for obstetricians. Chapter 5 is a good review of local anaesthetics in obstetrics but it is unfortunate that the chemical structure of lignocaine is different on successive pages. Section 3 deals with analgesia and anaesthesia for labour and delivery and includes chapters on birthing and psychoanalgesia, systemic medication, inhalational anaesthetics and ketamine and paracervical, pudendal and perineal field blocks. This section was interesting and adequately described, but the inclusion of pharmacokinetics, anaesthetic uptake and distribution, MAC and the properties of individual inhalation agents seemed out of place in this type of textbook.

Section 4 on major regional anaesthesia gives a good and full description of the indications, contraindications and complications (and their treatment) of regional anaesthesia. All aspects of the techniques of spinal, lumbar epidural and caudal epidural anaesthesia are clearly described and there is a good portion on the use of text doses.

Section 5 deals with maternal complications and the first chapter concerns caesarean section and delivery. The various methods of regional and general anaesthesia for caesarean section are discussed and the problem of acid aspiration is well reviewed. The reviewer would, however, not agree that in an emergency situation, when the patient does not have a functional intravenous infusion and has no obvious veins, then it is preferable to institute a mask induction of general anaesthesia rather than waste time performing a 'cutdown'. The following three chapters are on the subject of maternal health complications, obstetric complications and obstetric shock, pulmonary disorders, haemorrhage and postpartum intensive care. Whereas these are of interest one would not normally expect to learn about these problems in a book of this type. Chapter 18 is a new addition and discusses anaesthesia for non-delivery surgery during pregnancy. This is an interesting chapter and describes anaesthesia for general surgery in the pregnant patient, for cerclage, for postpartum sterilization and therapeutic abortion. Section 6 describes disorders of fetal growth and development, fetal monitoring and fetal distress, and birth asphyxia and neonatal resuscitation; only the last chapter being of direct interest to the anaesthetist.

The authors state that 'society expects that modern obstetrics will ensure not merely birth of a live infant from a planned pregnancy, but a quality of newborn life consistent with our highest aspirations' and there is no doubt that their book will aid this expectation. The illustrations throughout are excellent, the tables are lucid and it is extremely well and extensively referenced with references ranging from 1847 to 1985.

The book is obviously directed to the North American market but it would be a useful addition to an obstetric or anaesthetic library. The individual purchaser, however, would be better advised to purchase one (or both) of the excellent British textbooks on the subject at a considerably smaller price.

I. T. Davie

Atlas of the Human Oocyte and Early Conceptus by Lucinda L. Veeck. Williams and Wilkins, Baltimore, 1986, 330 pages with figures and tables, £10.00

This is an excellent book for the embryologist or senior scientist of an IVF unit and will have benefits for all members of the IVF team, whether technical or clinical. It can be used for training new members of staff in the identification and tabulation of harvested oocytes and could also be used for reference purposes when one is unsure of the maturity of a particular oocyte or the quality of an embryo. It contains easily readable and comprehensive information on a large sample of human oocytes and pre-embryos with beautiful photographic examples of various stages of oocyte maturity and pre-embryo development. The stages covered in detail range from human oocytes at the time of follicular aspiration up to the cleaved human pre-embryo to the stage of normal replacement after in-vitro fertilization.

Further chapters show pictures of more advanced pre-embryos from the morula to blastocyst stages. Finally, and most importantly for clinical management, oocytes and pre-embryos demonstrating abnormalities of varying types are shown. Although experienced human embryologists would have seen other varieties of oocytes and pre-embryos, one would suspect that the great majority of types are represented in this book.

Whilst this book is an invaluable addition to the human reproduction literature, its cost will limit its availability and there is a need for a more comprehensive text of normal physiology and development of the oocyte and pre-embryo to make it more fully comprehensive.

Robert W. Shaw

Clinics in Anaesthesiology Vol 4: No. 1. Obstetric Analgesia and Anaesthesia pages 1–232; No. 2. Obstetric Analgesia and Anesthesia, pages 233–444 edited by G. W. Ostheimer. W. B. Saunders Co., London, 1986, £3.50 each.

Obstetric anaesthesia has not previously featured among the titles of *Clinics in Anaesthesiology* but the subject has been the focus of attention in two previous issues of *Clinics in Obstetrics and Gynaecology* from the same publisher. The first edition of *Clinics* devoted to the subject, in 1975, was edited by Bonica and subtitled ‘Recent advances and current status’; the second, in 1982, was edited by Rosen and subtitled ‘Safer practice’. The edition under review is a more expansive undertaking published in two volumes (in two successive issues). The editor’s stated objective is the presentation of a concise overview of obstetric anaesthesia that would serve for teaching and reference purposes now and for some time into the future.

In the first issue there are 19 chapters and British authors feature (jointly or exclusively) in only three of them. This leaves the ‘international cast of authors’ heavily weighted on the American side and contrasts with the 1982 *Clinics in Obstetrics and Gynaecology* in which the imbalance was in the other direction. There could hardly be a better opening than Bonica’s updated treatise on the pain of parturition. Despite the odd reference error, another highlight is the excellent resumé of current understanding of the practical applications, pharmacodynamics and -kinetics of intraspinal narcotics. Earlier enthusiasm has been tempered for one reason and another and if anyone wonders why nothing more has been heard about intrathecal β endorphin for relief of labour pain since the favourable report from Japan in 1981, an answer is given by the revelation that the cost of each dose is around $10 000! Other chapters consider maternal physiology, perinatal pharmacology and the various approaches to obstetric analgesia and anaesthesia (including non-pharmacological methods), systemic medication, paracervical and pudendal nerve block, spinal anaesthesia and general analgesia and anaesthesia. Interspersed, in no particular order, are chapters which examine various complications including gastric aspiration, toxic reactions to local anaesthetics, failed intubation and drug interactions. Some repetition must be accepted as inevitable but it seems unnecessary to have substantial comment on prophylaxis against acid aspiration syndrome in the chapter on general analgesia and anaesthesia when there is a chapter specifically devoted to the prevention and treatment of gastric aspiration.

A preponderance of American authors is again evident in the 15 chapters of the second issue, which is devoted to the anaesthetic management of various clinical entities including cardiac and respiratory disease, diabetes, hypertension, preterm labour, breech presentation and multiple pregnancy. Appropriately, the first chapter presents a cautious and serious look at the evidence of harmful effects on pregnancy of some anaesthetic practices and agents (including nitrous oxide). This must be one of many areas in which co-operation between obstetricians and anaesthetists is essential to resolve controversies and improve practices in both disciplines. Perhaps the recruitment of a few obstetricians as co-authors would have served the editor at least as well as his declared policy of encouraging senior authors to include a junior co-author, anticipating that the latter will provide a firm basis of authors on which to build for the next update. There may be a risk that perpetuation of a text written exclusively by obstetric anaesthetists for obstetric anaesthetists will detract from the understanding and co-operation between obstetricians and anaesthetists which must be promoted in the interests of their common patients. The editor’s own (joint) contributions on the nature and management of hypersensitivity reactions and neonatal resuscitation are perhaps not strictly either obstetric or anaesthetic topics but they are both suitable and commendable inclusions. Aptly the last chapter provides an international overview of obstetric anaesthesia. The improvement of services in developing countries poses a daunting challenge and there is room for much more improvement yet, even in the United States and United Kingdom.

Although these two issues of *Clinics in Anaesthesiology* are aimed primarily at anaesthetists they should be regarded also as a welcome addition to the obstetric literature. They certainly deserve a place in the library of any hospital that provides comprehensive maternity services.

R. P. Husemeyer

Transsexualism and Sex Reassignment edited by William A. W. Walters & Michael W. Ross. Oxford University Press, Oxford, 1986, 191 pages with figures and tables, £17.50

Transsexuals, we are told, are more common in Australia because of the relatively rigid sex role stereotyping that prevails there. This book is a product of a multidisciplinary team that deals with transsexuals in Melbourne. Between 1976 and 1982 this team has been involved in 68 sex reassignment operations for male-female transsexuals. There are some useful chapters, in particular on gender identity disorders of childhood, speech therapy for transsexuals, sex reassignment surgery from the viewpoint of both the surgeon and nurse, and legal aspects.

The strength of this small book is in its advice on practical management; its dealing with theoretical issues and aetiology is less convincing and there is too much repetition from chapter to chapter. Professionals working in this field will find something of value here.

John Bancroft

Books received some of which may be reviewed at a later date

Clinical Obstetrics edited by Carl J. Pauerstein. John Wiley & Sons, Chichester/New York, 1987, 1017 pages with figures and tables, £38.45

Common Problems in Obstetric Anesthesia edited by Sanjay Datta & Gerard Ostheimer. Year Book Medical Publishers, Inc, Chicago/London, 1986, 496 pages with figures and tables, £38 50

The Control of Human Fertility Second Edition edited by John F. Porter. Blackwell Scientific Publications, Melbourne, 1986, 315 pages with figures and tables, £9.50

Prevention of Preterm Birth: New Goals and New Practices in Prenatal Care (Colloque Inserm, Vol 138) edited by E. Papiernik, G. Breart & N. Spira. Available from Inserm, Institut National de la Santé et de la Recherche Medicale, 101 rue de Tolbiac, 75654 Paris, Cedex 13, 457 pages with figures and tables, Fr 200

Prescribing in Pregnancy edited by Peter C. Rubin. British Medical Journal, 1987, 126 pages. Available from British Medical Journal, British Medical Association House, Tavistock Square, London WC1H 9JR. £5.95 (UK), £7.50 (Overseas), $11.50 (USA including postage, by air abroad)

Infertility: A Guide for the Anxious Couple by Mary Anderson. Faber & Faber, London, 1987, 93 pages illustrated, £3.95 (UK), $6.95 (USA)

Where to be Born? The Debate and the Evidence by Rona Campbell & Alison Macfarlane. Available from National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford, OX2 6HE, £2.00

Aids to Obstetrics and Gynaecology (For MRCOG Part 2) Second Edition by Gordon Stirrat Churchill Livingstone, Edinburgh, 296 pages, £6.95

Manual of Obstetrics: Diagnosis and Therapy Second Edition edited by Kenneth Niswander. Little, Brown & Company, Inc., Boston, 1987, 465 pages with figures and tables, £9.95

Cancer of the Cervix: Diagnosis and Treatment edited by Hugh M. Shingleton & James W. Orr. Churchill Livingstone, Edinburgh, 1987, 327 pages fully illustrated with colour plates, figures and tables, £40.00

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution, major changes will be agreed with the author(s)

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Two copies of the manuscript and illustrations should be sent Manuscripts should be typed double spaced on one side of the paper, with wide margins. The names of author(s) and their appointment(s) and addresses at the time of preparation of the manuscript should be given. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss.

Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part Two further sub-divisions, with appropriately less significant headings, can be used, the third order heading runs on with text at a paragraph opening Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables. The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s)

Case reports and short communications do not require a summary or introduction Short communications should not exceed 600 words and contain no more than one table or figure

Tables and figures
Tables and figures should be separate from the text, with their positions indicated in the text margin Both are numbered with arabic numerals Colour illustrations are allowable only in special circumstances and the author will be expected to meet the cost of reproduction

Figures should be marked on the back (light in pencil) with the name(s) of the author(s), the figure number, and the top indicated Each should have a descriptive legend typed on a sheet separate from the figure Photographs should be unmounted glossy bromide prints of good contrast.

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc Tables are not included in this classification and should not be submitted as photographs Original X-ray films should not be sent—glossy prints must be submitted

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column)

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself

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Units and abbreviations
Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg) If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors Standard abbreviations, without punctuation, are used. *Units, Symbols and Abbreviations* (1977) published by the Royal Society of Medicine provides a useful guide Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics
Authors should describe clearly the design of their investigation and the source of the data All statistical methods should be specified so that it is clear which was used where Papers omitting this information may be returned without review The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else

Some points of detail to note are

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic
(2) The use of confidence intervals is encouraged
(3) The symbol ± should not be used when presenting SE or SD Presentation such as 'the mean was 14·2 (SD 3·2) mg' is preferred
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
(5) Unusual methods of analysis should be described and/or referenced

Authors are referred to the general statistical guidelines of Altman *et al* (1983) for advice about the presentation and interpretation of the statistical aspects of their research

Altman, D G., Gore, S M., Gardner, M J & Pocock, S J. (1983) Statistical guidelines for contributors to medical journals *Br Med J* **286**, 1489–1493

Human experiments
Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References
In the text, use the name of the author(s) followed by their date of publication; where there are two authors use the form Smith & Brown 1972; where there are more than two authors use Robinson *et al* 1979

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers In the case of books the order is: Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers Where appropriate, the chapter title and the names of the editors should be given

References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references Examples of the style to be used are given below.

Trudinger, B J , Lewis, P J & Petit, B (1979) Fetal breathing in intrauterine growth retardation *Br J Obstet Gynaecol* **86**, 432-436

Hytten, F E. & Leitch, I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p 26.

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Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent Only essential corrections can be accepted, more extensive alterations, which may delay publication, will be charged to the author Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed card sent with the proofs

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OXFORD · LONDON · EDINBURGH · BOSTON · PALO ALTO · MELBOURNE

Printed in Great Britain by Headley Brothers Ltd The Invicta Press Ashford Kent and London

Volume 94, Number 9, September 1987

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British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten

SUPER ARDUA

Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications

BJOGAS 94(9) 833–928 1987 ISSN 0306-5456

British Journal of Obstetrics and Gynaecology

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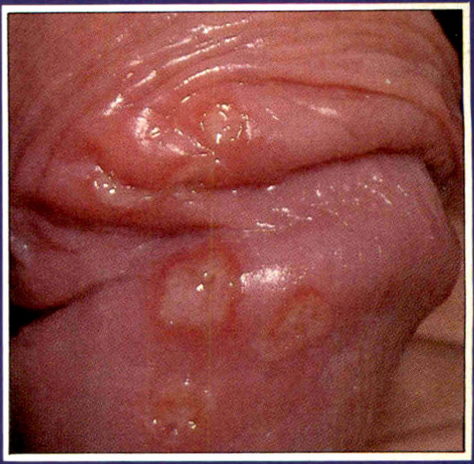

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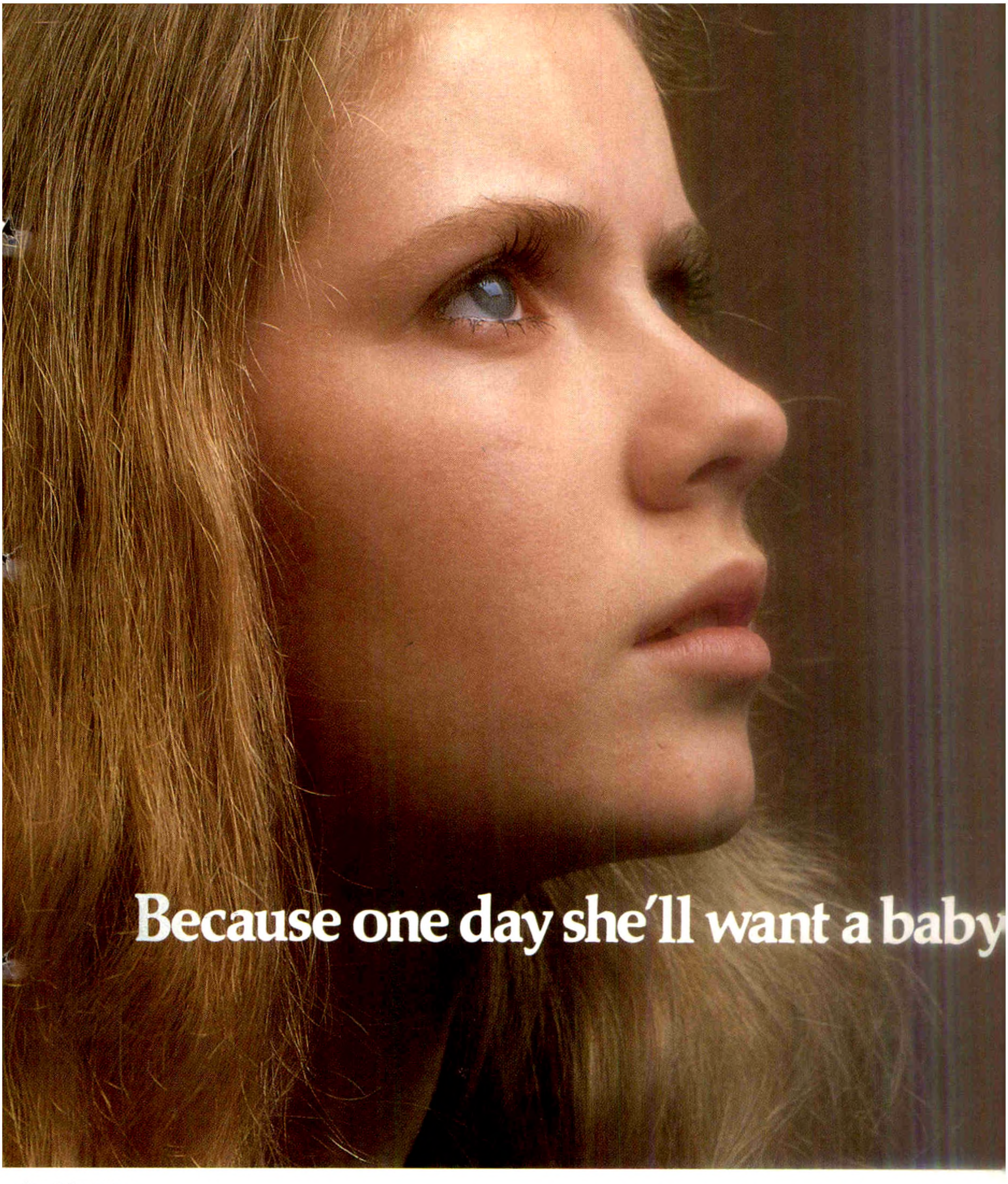
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36) £82.50 per box. **References:** 1. Harlap,S. *et al.*, *N.Eng.J.Med.*,
79, **301,** 677. 2. Richardson,J.A. & Dixon,G., *Brit.Med.J.*, 1976, **1,**
03. 3. Chen.J.K. & Elder,M.G., *Obstet.Gynecol.*, 1983, **62,** 339.
Christensen,N.J., Bygdeman,M. & Green,K., *Contraception*, 1983,
(1), 51. Cervagem is a trade mark. Further information is available
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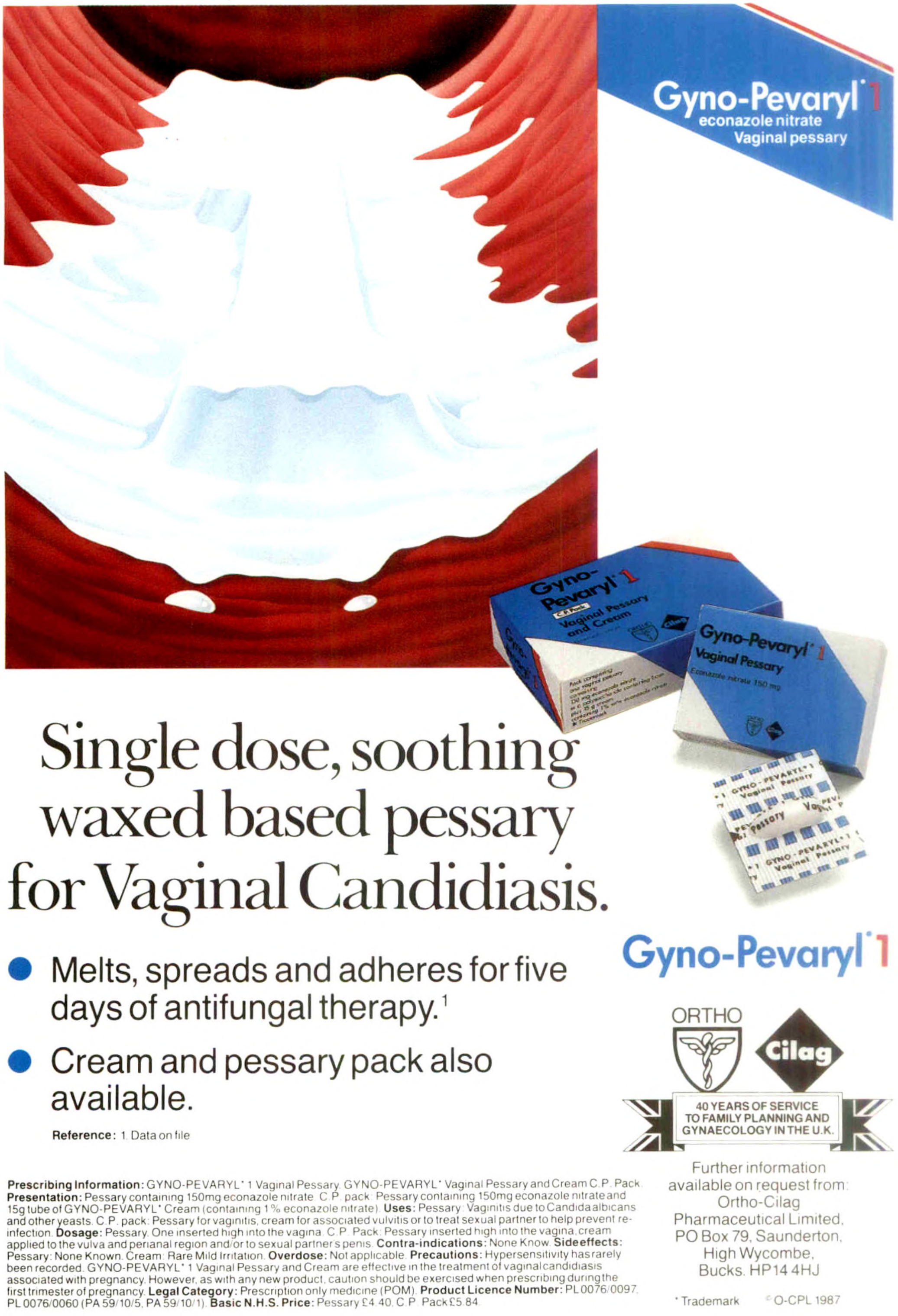

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References

1 Franks, S et al - J Endocrinol, (1985) 104 p 34 Abst 41
2 Yen, S S C et al J Clin Endocrinol, Metab (1970) 30, pp 435-442
3 Data on file
4 Ginsburg, J et al "Ovulation and Pregnancy after pure FSH Therapy in Sclerocystic Ovarian Change" XIth World Congress of Gynaecology & Obstetrics
5 Braendle, W et al "Advances in Diagnosis and Treatment of Infertility" Ed V Insler and G Bettendorf (1981) pp 33-41, Elsevier, North Holland
6 Gocial, B Wu, C H et al Society for Gynaecological Examination 31st Annual Meeting, San Francisco (21-24 March 1984) Abstract No 279, pp 164

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ISSN 0269-5022

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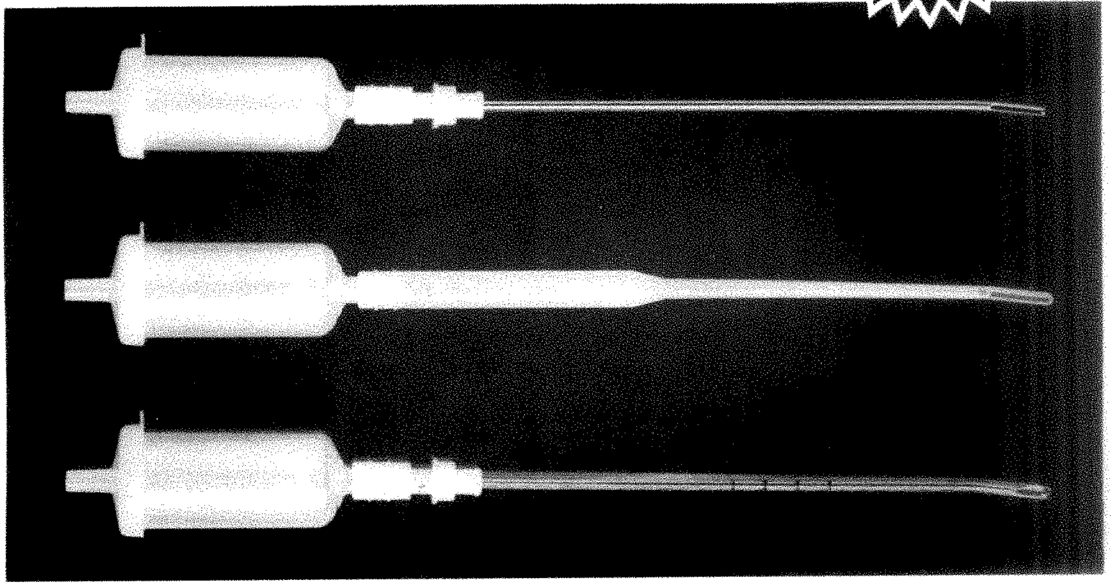

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COMMENTARY

In defence of the obstetrician

Many obstetricians feel under attack, from consumer associations on the one hand and increasing litigation on the other. When a pregnant patient presents a list of demands and insists on her chosen method of delivery, has the obstetrician the right to claim that he can offer special expertise and useful advice?

The conflict of approach arises partly from wider changes in social attitudes, including a general challenge to authority, the philosophy of 'doing your own thing' irrespective of the effect on others and the emergence of aggressive feminism as distinct from equal opportunity. Add to that the unsettling effect of the pace of change, and the way in which ideas and attitudes for good or ill are spread and influenced by the media.

The dilemma in obstetrics is well illustrated in the WHO booklet *Having a Baby in Europe* (1985) which is not a scientific publication but a report based on the discussion of a study group, which reads like a feminist midwife's protest. It is against the 'official medicalised' system which is assumed to be bad, and in favour of the alternative choice social system which must be good. The book presents a depressing catalogue of all the things that are considered wrong with the present methods but no evidence is given that the 'new' ideas have been better assessed and would be preferred by the majority of women. Ultrasound is dismissed as of unproven benefit yet concern is then expressed about respiratory distress in babies born prematurely by caesarean section. Relief of pain in labour is 'most often not an informed choice' and so by inference unhelpful, unnecessary or even damaging. Episiotomy is condemned because it can be associated with subsequent dyspareunia. In a discussion about current services the phrase 'A bulldozer is used to unearth disease whatever the cost' indicates profound lack of understanding. There are useful messages including the plea for establishment of perinatal surveillance systems and for general agreement on basic definitions but the book as a whole could destroy the confidence of the normal pregnant woman simply looking for the best available care for herself and her baby. In colloquial terms this report would throw out the baby with the bathwater.

A recent presentation from the Royal College of Midwives entitled 'The Role and Education of the Future Midwife in the UK' shows a similar desire for radical change. The report presents the laudable aim of attempting to raise the status of the midwife, proposing an ambitious range of practical experience during training but the future role of the midwife includes the suggestion that the pregnant woman or the woman who is contemplating pregnancy should normally refer herself directly to a midwife. None of us exists in isolation and there are dangers in bypassing the general practitioner who has traditionally been the co-ordinator of all forms of medical care in Britain. Improvement in the status of the midwife would perhaps be better achieved by encouraging those who are able, and have acquired the training, to take on further responsibility and an increasing share of antenatal, intrapartum and postnatal care both in hospital and community service, but with the emphasis remaining on teamwork. Incidentally the report would not take any prizes for plain English; e.g. the educational ideology includes the intention to 'centre the client as the pivotal point for the understanding and development of caring skills'—presumably meaning learning to care for the patient.

Marjorie Tew (1986) has made earnest attempts to prove that home confinement is safer than hospital delivery with its iatrogenic risks. However, is it not only a vocal minority who press for home delivery? Will the home confinement midwife and doctor not also be human, and liable to errors of omission as well as commission like their counterparts in hospital? Much that is known about failings of care in hospital is a consequence of very thorough 'in house' monitoring which is not such a strong feature of domiciliary obstetrics.

The obstetrician's best response lies in two approaches: (i) to continue and intensify the maternal and perinatal mortality and morbidity studies which reflect a constant process of appraisal and search for improvement and (ii) to undertake controlled trials wherever possible and ethical, in order to assess whether new methods, ideas or equipment are better than those existing.

With prompting from Iain Chalmers, controlled trials in specific aspects of obstetric care are being undertaken and should be encouraged. The best recent example is the assessment of chorion villus biopsy, and others include cervical cerclage and bed rest for twin pregnancy. Not all problems lend themselves to a scientific or statistical approach and there is always the difficulty of what to do with a particular patient here and now. But this scientific approach is the way to progress, and there is no evidence that alternative systems are better.

The emergence of a pressure group usually indicates a need for change, improvement or better explanation. But we should change clinical practice only as scientific evidence of benefit accumulates, discarding those policies which are not beneficial. To jump on every popular bandwagon as the WHO booklet reflects would be the negation of this logical progression.

The Clarendon Wing of the General Infirmary covering the Western District in Leeds opened in 1983 and contains virtually all the obstetric and paediatric beds in the District. Obstetric cases have risen by 40% in 4 years. Our patients by voting with their feet indicate the local appreciation of the service. Our current annual perinatal mortality rate, including congenital abnormalities, is 5·8. We offer a 24-h epidural service on request, and with 90% intrapartum fetal monitoring, intrapartum asphyxia has disappeared. The induction rate is 5·9% and the caesarean section rate is 12%. The paediatricians achieve miracles every week with the premature babies. Such practice merely reflects what is happening all over the country. Can Leboyer or Odent produce better figures for an entire city or region?

A teaching and examination system which continues to introduce advances in basic science into clinical practice helps to maintain steady progress. The social factors in obstetric care and outcome are well recognized by hospital as well as by domiciliary staff and information on this aspect is increasingly applied to the organization of care. Political and social measures designed to improve the health of the nation as a whole are clearly welcome and beneficial.

Obstetricians and paediatricians are as sensitive as any group to the emotional needs of their patients. A useful aspect of recent change in authoritarian attitudes is that hospitals are progressively less threatening and more homely. Many patients wish for more information and fuller consultation before decisions are taken. This is entirely appropriate, but at the end of the day should the obstetrician do as the patient wishes or stand by his or her own opinion?

What of the patient who insists against advice on having the baby at home, standing up, supported by her partner and claiming that the emotional fulfilment transcends all other priorities? Such a patient should be invited to consult another doctor who may be more in tune with her ideas; if there is not mutual respect and understanding between patient and doctor it is not in the patient's best interest to continue the relationship. Let those, who wish, arrange a new study or trial of home delivery or of special 'low tech' facilities if they can. Meanwhile the modern obstetric hospital can accommodate most personal preferences, including free movement in labour with telemetry, initiation of breast-feeding immediately after delivery, and domestic type furnishings in some delivery rooms (Beard & Capel 1985) without losing the first objective of the best chance of a live and healthy mother and baby. Those of us familiar with Flying Squads have no wish to revert to the risks of routine domiciliary obstetrics.

Another important source of pressure on the obstetrician is the rising trend of litigation (Frazer 1987). There is the assumption that there must be a cure for every medical ailment, and that if something goes wrong it must be someone's fault. The threat of litigation creates pressure to take every possible precaution and is relevant as one factor tending to increase medical supervision and operative intervention, such as readier resort to caesarean section for breech presentation, while the 'social' pressure is the other way to reduce supervision and intervention. The best protection for the doctor remains the one of talking to the patient and recording an outline of what is said. For the genuine accident we must surely progress to a no-fault insurance-based compensation scheme whilst retaining the patient's right to sue for true negligence. There should be prompt and fair compensation for the degree of injury and a greater willingness on the part of the doctors to explain what went wrong.

Hall (1987) has recently put the case for the obstetrician to focus on medical indications when a woman asks for a caesarean section. In a delightful 'Personal View' on the theme 'It is my body. I can do what I want with it', Philipp (1986) was concerned with the patient's own best long-term interest. One might add 'Yes, of course you can but especially when you are pregnant, freedom and rights have to be balanced by duties and responsibilities, for at least one other individual is involved'.

Where does that leave us? Obstetricians and neonatal paediatricians are doing a good job, and while listening carefully to their patients, they should continue the steady process of adapting and improving what is a sound, scientific and humanitarian service. More time to discuss and explain obstetric objectives and policies would be welcomed by all but will require more obstetricians!

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British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 836–842

Pregnancy following induced abortion: maternal morbidity, congenital abnormalities and neonatal death

ROYAL COLLEGE OF GENERAL PRACTITIONERS/ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS JOINT STUDY

P. I. FRANK, C. R. KAY, L. M. SCOTT, P. C. HANNAFORD, D. HARAN

Summary. In a prospective cohort study of the long-term sequelae of induced abortion, a comparison is made between a group of 6418 women who had an induced abortion (cases) and a control group of 8059 women recruited with an unplanned pregnancy which was not terminated with an induced abortion (controls). The present paper reports on 729 cases and 1754 controls who had a post-recruitment pregnancy. In general, prior induced abortion had no material effect on the rate of pregnancy-related morbidity, nor on the rate of congenital abnormalities and neonatal death in the offspring. There was, however, a significant difference in two specific conditions. In the post-index pregnancy in the cases there was an increased relative risk (RR 2·26) of the occurrence of urinary tract infection and a decreased risk (RR 0·25) of pregnancy-related anaemia.

Reports of the complications of childbirth following induced abortion have shown conflicting results (Hogue *et al.* 1982). Most studies have been retrospective and suffered the disadvantage of selective recall by patients of previous induced abortion. Some have failed to adjust for important predisposing conditions or have been without appropriate controls

The present long-term, prospective cohort study aims to compare the subsequent health of a group of women referred by their general practitioner and having an induced abortion (cases) with that of a group presenting to the same doctors with an unplanned pregnancy and not having an induced abortion (controls).

Analyses of the early sequelae of induced abortion and the outcome of pregnancy (including shortened gestation and low birthweight) following the operation have been described previously (Frank *et al.* 1985; Frank 1985; Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists 1985). The present communication concerns occurrence of morbidity in the mother and congenital abnormalities and neonatal death in the baby associated with the first post-recruitment pregnancy. Only pregnancies continuing beyond 28 weeks gestation are considered in this paper.

Subjects and methods

Detailed accounts of the methods and the characteristics of recruited women have been published elsewhere (Kay & Frank 1981). In summary, between 1976 and 1979, 1509 general

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practitioners from England, Scotland and Wales recruited 6418 cases and 8059 controls, and 795 gynaecologists to whom recruited women were referred for induced abortion provided information about their consultation and the operation.

General practitioners completed a recruitment form for all cases and controls with details of age, marital status, the present pregnancy, past obstetric history, previous medical history, ethnic origin and smoking habits. Classification of occupation is an unsatisfactory method for determining social status in young unmarried women. Pilot trials showed that the age at which full-time education was completed correlated well with occupational data. Thus, educational characteristics which are applicable to all subjects were used in the study as a measure of social status.

Gynaecologists recorded information about their consultation and, if they agreed to termination, gave details of the operation. The general practitioners provided information about the outcome of control pregnancies on a special form sent to them 10 months after the last menstrual period.

The general practitioner has completed a follow-up form for each patient every 6 months from her date of recruitment. Information is recorded about all newly presenting episodes of illness reported over the previous 6 months, changes of partner, death of the patient, or the date when she left the practice (when a patient leaves the practice in which she was recruited she is withdrawn from further observation). New pregnancies are also notified and, if referred for induced abortion, the gynaecologists concerned are asked for the same details as for the index pregnancy. Observation over at least 10 years is planned.

The term index pregnancy refers to that at recruitment and the 'post-index' to the one subsequent to the index.

Subjects included in the analysis

All recruited patients, whether cases or controls, who had documented records of post-index pregnancies continuing beyond 28 weeks gestation were included in the analysis.

Classification of morbidity

Total pregnancy related maternal morbidity, congenital abnormalities and neonatal deaths in the offspring were analysed as 'present' or 'absent'. In addition, specific pregnancy related categories or groups of categories were examined separately where the number of occurrences justified the analysis. The sole criterion for the diagnosis of specific morbidities was that they were present in the medical records held by the general practitioner, whether made by the hospital or the family doctor. Morbidity was coded according to the International Classification of Diseases (8th Revision) 1965. For the purpose of analysis these were grouped as follows:

a) Haemorrhage before labour (including one or more occurrences of placenta praevia, premature separation of placenta, threatened abortion and all other haemorrhage).
b) Anaemia of pregnancy.
c) Urinary infections.
d) Pre-eclampsia, toxaemia.
e) Labour complicated by one or more occurrences of antepartum haemorrhage, placenta praevia, retained placenta, postpartum haemorrhage.
f) Malposition, malpresentation, cephalopelvic disproportion, prolonged labour.
g) Trauma at delivery.
h) Forceps delivery.
i) Caesarean section.
j) Fetal distress.
k) Congenital abnormality.
l) Neonatal death.

The above categories are not mutually exclusive.

Loss to follow-up

Loss to follow-up occurred almost exclusively when patients moved from their doctor's list, usually when moving from his area, or when a doctor withdrew from the study. In the present analysis, 10 years after the start of recruitment, 2462 cases and 3454 controls were still under observation (38% and 43%, respectively, of the originally recruited population). The characteristics of patients lost to follow-up have been analysed and compared with the total population. Patients no longer under observation were slightly younger, had a lower parity, slightly higher educational class and contained more single women than the original study population. These findings applied equally, however, to cases and controls, so that the losses modified only to a minor extent the comparisons between the original study population. In any case, allowance has been made in the statistical analysis for variations in recorded characteristics of the residual subjects.

It would be a matter of concern, however, if there was a suspicion that patients lost to follow-up were atypical in respect of characteristics which have not been recorded. Personality differences would be particularly important. It has been argued that differences in cigarette smoking would be an expression of personality differences (Royal College of General Practitioners 1974). It is reassuring, therefore, to find that the smoking habits of patients lost to follow-up were almost identical to those of the total population.

Adjustment for confounding factors

A number of factors other than induced abortion may affect the complications of childbirth, and allowance must be made for these if they are likely to distort the results. In order to maximize the power of the analysis to detect differences between cases and controls, it is important to keep stratification within the statistical analysis to a minimum consistent with adequate control of confounding factors. An examination was, therefore, carried out of the effect of a number of variables on the maternal complications of childbearing in the post-index pregnancies of cases and controls combined as one group. The variables examined were: age; smoking; marital status; educational status; height; parity; and mental illness before recruitment. A variable was considered for inclusion in the stratification if there was a significant association ($P<0{\cdot}05$) between that variable and any one of the complication measures (Bradford Hill 1971). However, it only entered the stratification if there was also a material difference in the distribution of that variable between cases and controls. The variables selected in this way were age, parity and previous mental illness. Although it did not affect the complication rates significantly, smoking was also included as a variable as it was found to be an important factor affecting early morbidity following induced abortion in a previous analysis (Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists 1985). The relative risk of complications in cases compared with controls was estimated using the Mantel Haenszel procedure (Mantel 1963). The 95% confidence intervals were estimated using Mietinen's test base limit (Breslaw & Day 1980).

We can give an indication of the power of the study to demonstrate differences in rates between cases and controls as follows. There is a 90% chance of detecting a rate of 10% in the cases compared with 5% in the controls. If the rate in controls were 50% there is a similar ability to detect a rate of 55% in the cases. Both differences would be statistically significant at the 5% level of probability.

Comparison groups

For the main analyses the post-index pregnancies in the cases were compared with the post-index pregnancies in the controls with statistical adjustments being made for important confounding variables, as described above. The two groups, however,. had such different parity status (cases had 60% nulliparous women compared with 5% in the control group) that statistical adjustment may have been inadequate. Furthermore, parity reflects not only the number of full-term pregnancies but also the risk of complications within those pregnancies. For this reason, three other comparisons were also made.

In the first, women who were in their first pregnancy at recruitment were excluded, thus improving comparability of parity as both groups had at least one pregnancy before recruitment. This adjustment, however, excluded 60% of available cases. In the second comparison, post-index pregnancies of cases were compared with the index pregnancies of controls. This had the advantage not only of including more nulliparous control patients but also of increasing the power of the analysis by having 6261 women in the control group (all women recruited as controls for whom full details of the course and outcome of the index pregnancy were available). As there was a likelihood of under-reporting of those early pregnancy complications occurring before recruitment, the most common, that of threatened abortion, was excluded from this analysis. In the third comparison the post-index pregnancies of cases were compared with the index pregnancies of controls in those women whose index pregnancy was their first. This compared two groups of equal parity which differed in that cases had experienced one previous induced abortion. The effect of complications in previous pregnancies was thus avoided (women with bleeding before the induced abortion were excluded from the analysis).

Adjusted parity comparison

It is known that a normal pregnancy is associated with a reduced complication rate in subsequent pregnancies. To determine if an induced abortion offers a similar benefit a further comparison was made where the index pregnancies of cases (all of which ended in induced abortion) were counted as full-term pregnancies, and an appropriate adjustment made to the parity. Thus, cases with a real parity 0 were compared with controls parity 1, and cases parity 1+ with controls parity 2+

Results

Comparison of the post-index pregnancy of cases with the post-index pregnancy of controls showed no significant difference in pregnancy complication rates, the relative risk being 0·97 (95% confidence interval 0·86–1·10) (Table 1). The other comparisons carried out to allow for parity imbalance in the main analysis all showed similar non-significant differences.

Exclusion of women in their first pregnancy at index gave the relative risk for cases of 1·14 (95% confidence interval 0·88–1·47). Comparison of post-index pregnancy of cases with the index pregnancy of controls produced a relative risk of 1·02 (95% confidence interval 0·87–1·20), and when this comparison included only women in their first pregnancy at recruitment the relative risk was 0·99 (95% confidence interval 0·79–1·25).

Thus, the marked difference in parity between the comparison groups in the main analysis did not have any material effect on the overall results. For this reason analyses for the effect of induced abortion on specific complications in a subsequent pregnancy were investigated by comparing only the post-index pregnancy in cases with the post-index pregnancy in controls.

Adjusted parity comparison

When the parity of cases was adjusted to count the induced abortion at recruitment as a full-term pregnancy there was a significant difference in complication rates between cases and controls, the relative risk being 1·62 (95% confidence interval 1·35–1·94) indicating that induced abortion does not have the beneficial effect on the next pregnancy which is conferred by a full-term pregnancy (Table 1).

Specific pregnancy-related conditions

Various groups of maternal morbidity were examined (Table 2). The only statistically significant findings were in urinary tract infections, where the relative risk of cases to controls was 2·26 (95% confidence interval 1·29–3·95, *P*<0·01), and anaemia where cases had a relative risk of 0·25 compared with controls (95% confidence interval 0·07–0·84, *P*<0·05).

Table 1. Total pregnancy-related morbidity in post-index pregnancy of cases compared with controls and adjusted parity comparison‡

	Cases		Controls			
Comparison	Population	Observed number	Population	Observed number	Adjusted relative risk†	95% Confidence interval
Total	729	340	1754	651	0·97	0·85–1·10
Parity adjusted‡	729	340	1657	593	1·62**	1·35–1·94

** *P*<0·01.

† Relative risk adjusted for age at last menstrual period, parity, smoking at recruitment and mental illness before recruitment.

‡ In this analysis the parity of cases was adjusted to count the induced abortion at recruitment as a full-term pregnancy so that cases with real parity 0 are compared with controls parity 1 and cases parity 1+ with controls parity 2+

Table 2. Specific complications in post-index pregnancy of cases compared with controls

Complication	Cases (*n* = 729) Observed number	Controls (*n* = 1754) Observed number	Adjusted relative risk†	95% Confidence interval
Haemorrhage before labour	28	65	0·94	0·53–1·65
Anaemia of pregnancy	6	37	0·25*	0·07–0·84
Mental illness	9	26	0·54	0·23–1·27
Urinary infections	40	46	2·26**	1·29–3·95
Pre-eclampsia, toxaemia	45	81	0·80	0·49–1·30
Haemorrhage in labour	21	54	0·73	0·36–1·47
Disproportion	95	125	1·12	0·80–1·56
Trauma at delivery	68	106	0·94	0·61–1·45
Forceps delivery	76	70	1·01	0·64–1·60
Caesarean section	54	123	0·72	0·48–1·09
Fetal distress	25	27	0·91	0·43–1·93

* $P<0{\cdot}05$; ** $P<0{\cdot}01$.

† Relative risk adjusted for age at last menstrual period, parity, smoking at recruitment, and mental illness before recruitment.

Congenital abnormality and neonatal death

Comparison of the rates of congenital abnormalities in the post-index pregnancy of cases with controls (Table 3) produced a relative risk of 0·81 (95% confidence interval 0·41–1·60) and when neonatal death rates were examined, the relative risk was 0·84 (95% confidence interval 0·39–1·82) (Table 3). Neither was statistically significant.

Discussion

The results of the present study support the finding of other investigators (Chung *et al.* 1983; Madore *et al.* 1981; Harlap & Davis 1975) that induced abortion has no significant effect on the overall maternal complication rate of childbearing, or on the rate of congenital abnormality or neonatal death in the offspring in the subsequent pregnancy.

The prospective design of the present study minimizes problems suffered by retrospective studies of unreliable recall by patients of previous induced abortion (Schoenbaum *et al.* 1980; Chung *et al.* 1982) and also the under-reporting of early pregnancy complications (Hogue *et al.* 1982). A further advantage is that family doctors in the UK possess a comprehensive record of all reported morbidity, whether seen in hospital or primary health care setting and, thus, early complications, sometimes not seen in hospital, are more likely to be recorded.

Women who have an induced abortion possess a number of biological, social and behavioural characteristics which distinguish them from other women of the same age and parity (WHO Task Force on Sequelae of Abortion 1979). It is, therefore, impossible to find an ideal comparison group. One important feature is that almost all induced abortions occur in unplanned pregnancies, and it was to take

Table 3. Congenital abnormality and neonatal death in post-index pregnancy of cases compared with controls

Factor	Cases Population	Cases Observed number	Controls Population	Controls Observed number	Adjusted relative risk†	95% Confidence interval
Congenital abnormality	729	24	1754	56	0·81	0·41–1·60
Neonatal death	729	10	1754	23	0·84	0·39–1·82

† Relative risk adjusted for age at last menstrual period, parity, smoking at recruitment and mental illness before recruitment.

account of this that the control group was chosen to consist also of women with unplanned pregnancies.

Although 11% of cases had a post-index pregnancy at the time of analysis compared with 22% controls, there is no reason to believe that this difference should affect any complication rates of the post-index pregnancy, particularly as these rates were adjusted for important variables.

Adjustment was carried out for the most important confounding factors, namely age, smoking, parity and previous mental illness. These were determined by preliminary analyses. In addition, several different comparisons were performed to take account of the large parity differences between cases and controls and the resulting major inequality in complications in the preceding pregnancy. None showed any significant differences in pregnancy complication rates between cases and controls. The relative risk of cases to controls of 0·97 was consistent with that of 1·10 reported from a large prospective study in Hawaii (Chung *et al.* 1983).

The number of patients with post-index pregnancies is not yet sufficient to analyse the effect of various aspects of the induced abortion operation on the morbidity in the subsequent pregnancy, for example gestation, method of operation, place of operation.

To determine whether induced abortion reduces the complication rate in the next pregnancy to the same extent as a full-term pregnancy, a further comparison was carried out in which the induced abortion of the cases was counted as a full-term pregnancy. The significantly increased relative risk of 1·62 in the cases suggests that induced abortion does not offer the protection of a full-term pregnancy. This finding was again similar to that of the Hawaiian study (relative risk 1·64) (Chung *et al.* 1983).

When specific complications were examined, significant differences were found between cases and controls only in urinary tract infection and anaemia.

Urinary tract infection was more common in the induced abortion group with a relative risk of 2·26. This was independent of parity and also of a previous history of urinary infection. An examination of urinary infection unrelated to pregnancy also showed an increase in cases (to be reported). It is possible that this increase is partly explained by differences in sexual activity between the two groups.

There was a substantial reduction of anaemia in pregnancy in the cases. A number of factors could influence this difference, namely social class, inter-pregnancy interval and oral contraceptive use before the post-index pregnancy.

Social class differences were negligible between cases and controls having a post-index pregnancy. Neither was there a significant difference in the inter-pregnancy interval between the post-index pregnancies of the two groups. Thus, the possibility that a shortened inter-pregnancy interval would increase the likelihood of anaemia could not be an explanation for the difference between cases and controls. The use of oral contraceptives protects against anaemia (Royal College of General Practitioners 1974) and could decrease the rate of subsequent pregnancy-related anaemia. A comparison of the last contraceptive method used by cases and controls before their post-index pregnancy showed a significant excess in the proportion of Pill users in the cases (54·18%, $n = 729$; controls 41·96%, $n = 1754$ ($P<0{\cdot}05$). This factor could, therefore, explain the lower rate of anaemia in cases.

In contrast to the present study, two studies have reported a significant increase in the first trimester bleeding in the pregnancy following induced abortion. One concerned operations carried out before 1970 in Israel where abortion was illegal (Schoenbaum *et al.* 1980). The second found the increased risk only when the comparison was between women in their second pregnancy, one group with previous induced abortion, the second with a previous live birth (Harlap & Davis 1975). It is, therefore, likely that it was the protective effect of the full-term first birth rather than the induced abortion which caused the difference.

The association between induced abortion and placenta praevia in the subsequent pregnancy has been investigated by other workers with conflicting results (Barrett *et al.* 1981; Grimes & Techman 1984). The number of such occurrences available in the present study has not justified separate analysis. However, we have not found any increase in antepartum haemorrhage following induced abortion.

The finding that there was no significant increased risk in the offspring of congenital abnormality or neonatal death in the pregnancy following induced abortion confirms the findings of two other studies (Chung *et al.* 1983; Park *et al.* 1984). We have shown previously that there was no difference in the rate of stillbirth, low birthweight and shortened gestation (Frank *et al.* 1985).

An important question for those women who choose to abort their first pregnancy is whether the induced abortion increases the complication risks in the next pregnancy (Hogue *et al.* 1982). In order to determine this, the post-index pregnancy of cases and the index pregnancy of controls were compared, including only those women in their first pregnancy at recruitment. In effect, therefore, the comparison was between two groups of equal parity (PO) but with the group of cases having had an induced abortion compared with the controls who had no previous pregnancy. The risk in cases compared with controls was not materially different.

In conclusion, apart from an increased occurrence of urinary tract infection, the present results show no significantly increased risk of maternal morbidity, neonatal death or congenital abnormality in the pregnancy following induced abortion. However, as would be expected, an induced abortion does not have the beneficial influence on a subsequent pregnancy which is conferred by a pregnancy proceeding to full-term.

Acknowledgments

We are grateful to the following gynaecologists for their help and constructive criticism in the preparation of this paper: Mr S. L. Barron, Professor M. Elstein, Mr T. L. T. Lewis and Professor J. R. Newton. We wish to thank the Department of Health and Social Security, who are financing the study, and the general practitioners and gynaecologists who have been responsible for supplying the data which form its basis.

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Received 14 July 1986
Accepted 16 May 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 843–846

Ultrasound exposure time in routine obstetric scanning

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Summary. The duration of exposure to ultrasound was measured in 1274 patients having a routine examination during their first visit to an antenatal clinic. The measured median exposure time was 105 s. Since pulsed ultrasound was used (duty cycle of 1 in 800) the actual median maternal exposure time was 131 ms. Exposure of the fetus would usually be less since it rarely occupies the full width of the image. The relevance of exposure time to the safety of diagnostic ultrasound and the implications for users and manufacturers are discussed.

In recent years the safety of ultrasound has been questioned; many reviews of the available experimental and epidemiological data have been published and reassuring statements have been issued (RCOG 1984). Nevertheless, doubts remain about the wisdom of routine ultrasound scanning of obstetric patients. Such examinations are considered valuable for patient care, and as no consensus exists on what aspects of exposure might be important, they are likely to be continued. However, prudence dictates that the exposure should be kept to a minimum consistent with achieving the required information, which raises the question of what that exposure should be.

Exposure can be divided into two broad areas: first, the intensity and distribution of energy delivered by the transducer, and second, the time for which that energy is emitted by a transducer in contact with the patient. For exposure to ionizing radiation these two aspects are combined to give 'dose': the energy received per unit mass of tissue, which provides an index of tissue damage. However, when tissue is exposed to ultrasound different mechanisms have to be considered. Those most likely to cause significant bioeffects are heating, which is a function of the rate of energy flow (power per unit area), or mechanical processes such as cavitation which depend on many factors including the pressure amplitude of the acoustic field. Neither are known to be cumulative, although the temporal pattern of the exposure would determine any temperature rise. Hence dose in the ionizing sense is not appropriate and to date 'not even a definition of dose exists for ultrasound' (O'Brien 1986).

The report of a recent symposium (Kossoff & Barnett 1986) contains a concise survey of the present limited state of knowledge about the safety and standardization of ultrasound in obstetrics. From this it is evident that considerable work has been done on the definition and measurement of intensity, but even though Hill & ter Harr (1982) pointed out the need to include exposure time in any specification of exposure there is still a dearth of exposure time measurements in clinical conditions (Frizzell 1986; Preston 1986). Exposure time provides a maximum value for the 'dwell' time. This was defined by Carson (1980) as 'the maximum time that the ultrasound beam is held continuously in one place'; a more precise definition might attempt to exclude the effect of tissue movement. As no technique exists at present to measure dwell time in clinical conditions, measurement of exposure time provides the best alternative since it determines the upper limit of dwell time. This will provide a realistic basis for future experimental

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work, and should stimulate discussion on the minimization of exposure, during ultrasound procedures.

Materials and methods

Routine ultrasound is performed during the first visit to the antenatal clinic of the Queen Mother's Hospital to confirm a viable intrauterine pregnancy, assess gestational age accurately, and identify early pregnancy failure, twins and major fetal abnormality such as anencephaly. This study covered the period 22 August 1985 to 3 February 1986. All the scans in the clinic were carried out by one of two midwives trained in ultrasound (M.A. and M.W.) unless they were unavailable. Only scans performed by them were included in this study. The equipment used was a Dynamic Imaging Ltd (Dynamic Imaging Ltd, Young Square, Brucefield Industrial Park, Livingston EH54 9BX, Scotland) System XLP linear array scanner which incorporates two features pertinent to the study. Firstly, no ultrasound is emitted when the image is 'frozen' and secondly ultrasound transmission time is measured and recorded on screen, and optionally on a printer. Some additions and modifications to the System XLP were necessary. A sensor was added to detect when the transducer was in its holder, and another on the examination couch to indicate the presence of a patient. The software was changed by the manufacturer so that three measurements of time could be recorded. (1) The time a patient spent on the examination couch, which is referred to as the *consultation time* since the patient entered the room, sat on the couch, was scanned and all discussion took place while she was on the couch. (2) The *transmission time* when the transducer was active. (3) The patient *exposure time* which was the time that the transducer was active, out of its holder and the patient was on the couch.

These measurements were not displayed on the screen but were recorded by the printer and passed into a sealed box so that the measurements could not be seen by the operator and influence the performance of the scan. Comments on factors which it was thought might influence the scanning time were recorded on screen using the keyboard and then automatically transferred onto the printer. These factors included twins, a history of threatened abortion, a poor reproductive history, the presence of an observer in the room and bladder filling problems. If the patient's bladder required to be filled after an initial scan and the patient examined again, the exposure time was taken as the sum of the two separate exposures. Where an early pregnancy failure or fetal abnormality was detected, the patient was scanned again by a member of the medical staff in the main ultrasound department. This additional time was not recorded but the time for the first scan in the antenatal clinic was included in the analysis. The data collected from the printer after each clinic was transferred to the Glasgow University main frame computer and analysed using the SPSSX package (SPSS Inc., Suite 3000, 444 North Michigan Avenue, Chicago, Illinois, 60611, USA).

Results

There were 1274 patients in the study group with gestational ages ranging from 7 to 40 weeks (mean 14·8 weeks, 90% less than 20 weeks). The median consultation time was 6 min 46 s with a maximum of 22 min. The distribution of maternal exposure time is shown in Fig. 1, the median being 105 s and the maximum 9 min 37 s. The mean percentage of the consultation time during which exposure to ultrasound occurred was 29% (SD 12). The correlation coefficient between exposure and consultation times was 0·58 and in 70% of consultations lasting ⩾10 min, less than one third was occupied by actual ultrasound exposure.

In the 23 women who had to fill their bladder before they were scanned again, the median exposure time was 171 s, 63% more than the median for the whole group. In 10% of the study group (127 patients) exposure time was >3 min 33 s. In one quarter of these the recorded comments provided some explanation of the relatively long times. These included 7 of the 13 sets of twins; 12 of the 30 patients with bladder filling problems (including those with overfull bladders who required to empty them for comfort after the start of the scan); 7 of 21 late bookers; 2 of 3 patients with fibroids coexisting with pregnancy; and 5 of the 22 with early pregnancy failure; in the remaining three quarters comments, if any, did not provide any explanation of the longer time.

Discussion

The measurements in this study are of the time for which an active transducer was in contact with the maternal abdomen. If the fetus does not occupy

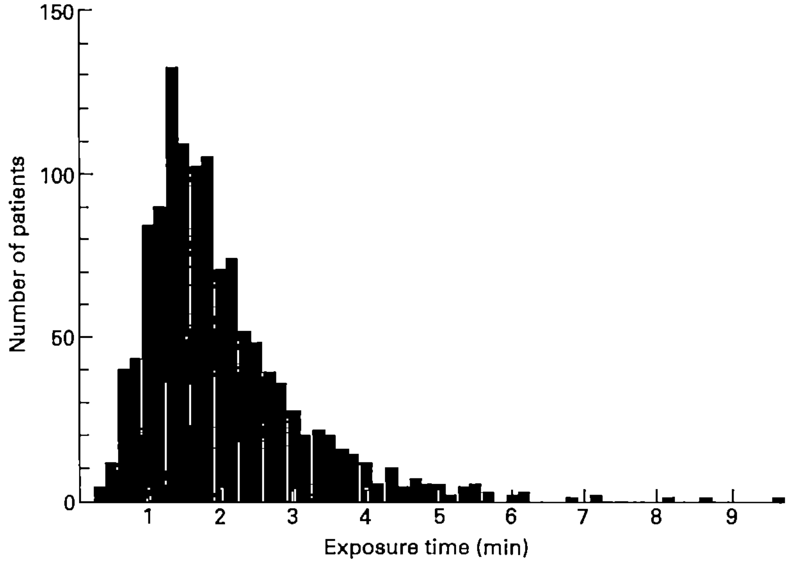

Fig. 1. Distribution of maternal exposure time, grouped in 10-s intervals $n = 1274$; median = 105 s; mean = 123 s, minimum = 18 s; maximum = 577 s.

the full image width it will only receive ultrasound for a fraction of this time. Bang (1986) discussed the susceptibility of the fetus to physical damage and suggested up to 5–6 weeks as being 'the stage of maximum sensitivity'. The crown–rump length of a 6-week fetus is about 6 mm and if, as in the XLP, the transducer has an active length of 116 mm the fetus would intercept approximately 5% of the acoustic energy. The fetuses in this study group ranged upwards from 50 days gestation. Selecting the 14 fetuses <8 weeks as an example near to the susceptible age (Bang 1986), it was found that the maternal exposure time ranged from 20 to 261 s, median 99·5 s. Taking the transducer length as 116 mm the fetal exposure times were calculated and found to vary from 1·9 to 30·3 s. Other factors directly affecting the exposure are the repetition rate and duration of the ultrasound pulses. These were measured by F. A. Duck (personal communication) on another XLP as 2604 Hz and 0·48 μs respectively. Using these values, the aggregated time during which ultrasound is being generated, given an exposure time of 105 s, is 131 ms, and in the case of the hypothetical 6-week fetus this could result in a maximum aggregated fetal exposure time of approximately 6·5 ms. Such calculations will depend on the particular instrument, the transducer characteristics and on the size and orientation of the fetus.

From our study it is not always clear why longer scanning times were required in some patients than in others; this aspect could be usefully investigated. It is also interesting to note that the consultation time is a poor estimate of actual ultrasound exposure time.

Carson (1980) estimated dwell time in examinations using sequential arrays (i.e. linear and curvilinear arrays) as 10–300 s. If this is taken to be the range of maximum dwell times, and assuming that he was considering obstetric scans, our study supports his estimate.

The only other measurements of clinical exposure time of which we are aware were recorded by Hall (1974) in the same hospital using a Diasonograph static scanner (GL Ultrasound Ltd, Royston Road, Deans Industrial Estate, Livingston EH54 8AH, Scotland). At this time the examinations were principally for biparietal diameter measurement and placental localization. Two methods of time measurement were employed, one gave an average 261 s for 848 patients, the other allowed the time distribution of transmitter output setting to be estimated. The second method resulted in somewhat higher values; 565 s in a group of 80 patients, with a maximum of 40 min for a placental localization.

It was noted that the higher average might be due to a higher than average number of these examinations in this particular group. Taking a representative value from the data by Hall (1974) of 6 min together with the pulse repetition rate of 250 Hz indicates that on average patients received 90 000 pulses of ultrasound. In our present study the number would be 273 000 i.e. 105s×2600 Hz. It would therefore appear that the reduction in exposure time from 360 to 105 s may have been achieved at the 'expense' of a three-fold increase in the number of acoustic pulses used. Such comparisons do not take into account the substantial improvements in the quantity and quality of the information obtained.

Even though the exposure times reported in this study appear short it will still be prudent, as suggested in the introduction, to minimize the exposure time. To achieve this goal, good scanning techniques are necessary if all the required information is to be obtained. This implies careful and thorough training of users. A positive approach to the minimization of scanning time could also be expected to improve the efficiency of the ultrasound service but should not be allowed to reduce its efficacy. The design of equipment will have a direct influence on patient exposure. This will tend to fall if (i) high quality images are produced since this will reduce the time required to recognize required features, (ii) control of sensitivity is effected by adjustment of transmitter output rather than receiver gain and (iii) emission of ultrasound is inhibited when the image is frozen as proposed by Meire (1981) thus avoiding unnecessary exposure, either when the transducer is left on the patient during measurements or during relocation of the transducer following its temporary removal.

The reduction of acoustic output levels is a complex issue. Measurements indicate that large differences exist between designs of machine intended for the same function. For example, considering only sequential array scanners (linear), the power and intensity outputs can vary more than 200 times while the maximum acoustic pressures can vary 100 times (Preston 1986; NCRP 1983). Since the use of 'high' outputs implies a reduced margin of safety their use should be questioned. If higher output is shown to provide significant improvement in imaging compared with 'low' output machines, their use may be justified to provide the necessary level of detail for certain procedures. It could be argued that their use should be avoided in routine examinations.

The conclusion that the total duration of fetal ultrasound exposure for a first visit obstetric scan is about 131 ms may seem reassuring but it should not lead to complacency. It may, however, be used as a guide for further research into the effects of ultrasound exposure. If any relevant biological effects are found which depend on the total quantity of acoustic energy then the time of exposure will be particularly relevant.

Acknowledgments

We would like to thank Professor C. R. Whitfield for his support, Mr J. Powell for modifying and maintaining the equipment and Mrs D. MacFadyen for assistance with the data preparation.

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Received 21 October 1986
Accepted 28 January 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 847–850

Evaluation of the WHO criteria for 75 g oral glucose tolerance test in pregnancy

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Summary. A group of pregnant women at high risk of developing diabetes in pregnancy had paired oral glucose tolerance tests (OGTT) using a 100 g load followed by 75 g load. When the World Health Organization (WHO) criteria and the National Diabetes Data Group (NDDG) criteria were compared, the 2-h plasma glucose value after the 100 g load was the most discriminative in differentiating those with normal glucose tolerance, impaired glucose tolerance and gestational diabetes mellitus. When only the 2-h plasma glucose values were assessed, the WHO test (75 g: 8 mmol/l) agreed with the NDDG test (100 g load: 9·2 mmol/l) in the diagnosis of glucose intolerance in 60% of subjects only. Using the same criteria at 2-h (8 mmol/l) the agreement between these tests was 47%. Reducing the glucose load from 100 g to 75 g produced a reduced glucose response in 49% of the subjects, with a significant decrease in the area under the glucose response curve.

The prevalence of gestational diabetes mellitus (GDM) around the world varies between 0·15% to 7·5% (Hadden 1985). This wide variation can not simply be explained by racial or geographical differences but could be due to the different criteria adopted in different centres to establish a diagnosis of GDM. Different criteria for diagnosing glucose intolerance in pregnancy using the oral glucose tolerance test (OGTT) have been proposed: a 3-h test after a 100 g glucose challenge (National Diabetes Data Group 1979); a 3-h test after a 50 g glucose challenge (Gillmer *et al.* 1975); a 2-h test after a 75 g glucose load (WHO Expert Committee on Diabetes Mellitus 1980) or a 3-h test after a glucose load related to the body weight of patients (Fajans & Conn 1965). This study investigates the maternal glucose response in a selected group of pregnant women who had a 100 g OGTT followed shortly by a 75 g OGTT and compares the different criteria applied to these tests of glucose intolerance in pregnancy

Subjects and methods

Pregnant women were selected for a 100 g OGTT because they had a past history of GDM, previous macrosomic infants (>4 kg), a positive family history, accelerated fetal growth in present pregnancy, recurrent glycosuria, maternal obesity (>120% ideal weight), and previous unexplained stillbirth or congenital abnormality. The diagnostic criteria proposed by the National Diabetes Data Group (1979) for the 100 g OGTT were used for plasma glucose: fasting, 5·8 mmol/l; 1-h, 10·6 mmol/l; 2-h, 9·2 mmol/l and 3-h, 8·1 mmol/l. Those women found to be abnormal by these criteria were

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recalled within 2 weeks for a 75 g OGTT. Venous blood was sampled at 0, 1, 2 and 3 h during both tests, and glucose levels were measured on venous plasma by a Beckman glucose analyser using the specific enzyme glucose oxidase (Beckman Instruments Inc., USA). The 75 g OGTT results were interpreted according to the criteria proposed by the WHO Expert Committee (1980) at 0 and 2 h. Women were then classified as having either normal glucose tolerance (NGT) or impaired glucose tolerance (IGT) or gestational diabetes mellitus (GDM).

Table 1. Indications for an oral glucose tolerance test in study subjects

Indications	*n*	%
Recurrent glycosuria	105	30
Accelerated fetal growth	103	30
Family history	41	12
Maternal obesity	39	11
Previous macrosomic infant	16	5
Previous gestational diabetes mellitus (GDM)	15	4
Polyhydramnios	8	2
Others	20	6

Table 2. Distribution of subjects using two different diagnostic criteria of abnormality at 2 h after paired oral glucose tolerance tests (OGTT)

	NDDG (100 g)	
WHO (75 g)	<9·2 mmol/l	≥9·2 mmol/l
<8·0 mmol/l	46	111
8–10·9 mmol/l	27	151
>11·0 mmol/l	0	12

NDDG, National Diabetes Data Group criteria, WHO, World Health Organization criteria.
Negative agreement = 46/347 = 13%; positive agreement = (151 + 12)/347 = 47%; overall agreement = 60%

Table 3. Distribution of subjects using the same criteria at 2 h (WHO criteria) for the two different glucose loads

	Plasma glucose level at 2 h with 100 g test		
Plasma glucose level at 2 h with 75 g test	<8·0	8·0–10·9	≥11·0
<8·0	27	109	21
8·0–10·9	7	128	43
≥11·0	0	5	7
Total	34	242	71

Both tests agreed in· (27 + 128 + 7)/347 = 47%.

The area under the glucose response curve was estimated in arbitrary area units (AAU) as the sum of the glucose concentrations minus ½ × (sum of the 0- and 3-h glucose concentration) (Harding *et al.* 1973). The AAU after the 100 g and 75 g OGTT were then compared.

Statistical analysis was by Student's *t*-test where appropriate.

Results

A total of 3084 pregnant women was screened with a 100 g OGTT and 401 (13%) of them were abnormal by the NDDG criteria. Of these 401 women, 347 had a subsequent 75 g OGTT as 54 defaulted from the 75 g test and were excluded from the study. The indications for performing the 100 g OGTT in these 347 women are shown in Table 1. The mean age of the women screened was 28·8 years (SD 4·3) and the mean gestational age at diagnosis of glucose intolerance was 29·2 weeks (SD 6·3). When the subsequent 75 g OGTT was interpreted by the WHO criteria, 157 (45%) had normal glucose tolerance, 178 (51%) had impaired glucose tolerance and 12 (3%) had gestational diabetes mellitus.

In order to compare the paired 100 g and 75 g OGTTs, the plasma glucose levels at 2 h after the glucose challenge were studied. When the women were grouped according to the different diagnostic criteria of the NDDG (9·2 mmol/l) and the WHO (8·0 mmol/l), glucose responses agreed in 60% (Table 2). When the two different glucose loads were compared using the same WHO criteria at 2 h, the results agreed in only 47% (Table 3).

The 347 pregnant women were divided by the results of 75 g OGTT, using the WHO criteria, into NGT, IGT and GDM groups and the mean glucose values from the 100 g OGTT are shown in Table 4. The fasting and 1-h glucose values were not significantly different between the three groups but the 2-h values were significantly different between all three groups. There were no differences in the 3-h glucose values between the NGT and IGT groups.

The arbitrary area units under the glucose

Table 4. Plasma glucose levels of the 100 g OGTT in the subjects grouped by the WHO criteria using the 75 g test

Time after load (h)	Plasma glucose level (mmol/l) Group I (normal GT) (*n*=157)	Group II (impaired GT) (*n*=178)	Group III (diabetes mellitus) (*n*=12)
Fasting	4·9(0·6)	4·9(0·6)	4·9(0·4)
1	11·2(1·3)	11·2(1·5)	12·0(2·3)
2*	9·4(1·6)	10·3(1·4)	12·7(2·5)
3†	8·2(1·6)	8·2(1·9)	10·1(2·7)

* At 2 h I *vs* II; I *vs* III; II *vs* III: $P<0·001$.
† At 3 h I *vs* III; II *vs* III: $P<0·001$; I *vs* II: Not significant.

Table 5. Area under glucose response curve (AAU) of subjects grouped by the WHO criteria

	Group I (normal GT) (*n*=157)	Group II (impaired GT) (*n*=178)	Group III (diabetes mellitus) (*n*=12)
After 100 g test (AAU)	27·2(2·0)	28·1(2·4)	34·2(4·7)
After 75 g test (AAU)	22·1(1·8)	24·9(1·9)	30·8(3·7)
P value	<0·001	<0·001	<0·05

Results are means (SD) values of arbitrary area units (AAU).

response curve after the 100 g and 75 g tests were correlated by the following equation (Fig. 1):

$$\text{AAU 75 g OGTT} = 8·02 + 0·57 \times \text{AAU 100 g OGTT}$$
$$r = 0·53,\ P<0·001$$

The mean AAU values after the 75 g test were significantly different from the values after the 100 g test in the groups of women classified as NGT, IGT and GDM; being about 3·2–5·1 units lower with the smaller glucose load (Table 5).

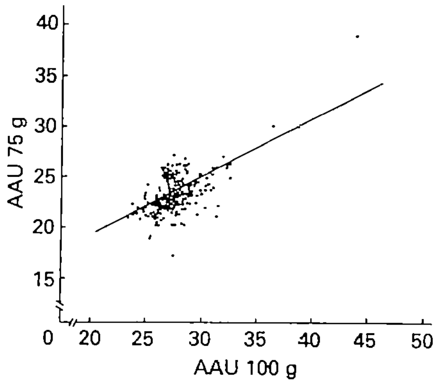

Fig. 1. Correlation between the arbitrary area unit (AAU) under the 75 g and 100 g glucose response curves. AAU 75 g = 8·02 + 0·57 × AAU 100 g, $r = 0·53$; $P<0·001$.

Discussion

The identification of the pregnant woman with glucose intolerance is controversial. Detailed comparison of data between centres has not usually been possible because diagnostic criteria were often different. The recommendations of the WHO Expert Committee on Diabetes Mellitus (1980) for the 75 g OGTT in pregnancy tried to correct this defect but it was noted during the Second International Workshop-Conference on Gestational Diabetes Mellitus, Chicago (1985) that more data were required on the 75 g OGTT in pregnancy. The present study shows that in a group of 'abnormal' patients identified by the 100 g OGTT, 45% were classified as normal by the 75 g OGTT. When the two diagnostic criteria were compared, the overall agreement of the two sets was only 60% (Table 2). Whether there is a need to treat these women, who have normal GT as judged by the WHO criteria, is the subject of another study. If treatment in this group of pregnant women with normal GT does not alter the perinatal outcome, this group of women can be regarded as 'overdiagnosed gestational diabetics'.

When the size of the glucose challenge was altered, maternal glucose response also changed. Using the same diagnostic criteria

(WHO), a 75 g test following a 100 g test agreed in only 47% of women (Table 3); 49% of the patients had a reduced glucose response when a lower glucose dose was given. These findings do not agree with the view that maternal glucose response is independent of the size of the glucose challenge (Castro *et al.* 1970). When the two tests were compared by the area under the glucose response curve, the areas after the 75 g test were significantly lower than those after the initial 100 g test.

The WHO diagnostic criteria for glucose intolerance in pregnancy use the same fasting and 2-h plasma values that are used for non-pregnant subjects. The WHO criteria have been criticized because they do not take into account the physiological fasting hypoglycaemia of pregnancy. Table 4 shows that fasting blood sugar level was not different between the groups, even in those with frank gestational diabetes by the WHO criteria, in which the cut-off value of 11 mmol/l at 2 h is a much stricter criterion than the 9·2 mmol/l used by the NDDG. When the results of the 100 g OGTT were analysed, only the plasma glucose level at 2 h was discriminative in differentiating the three groups of women classified by the WHO criteria. This discriminative power of the 2-h OGTT had been shown previously to be comparable to that of the 3-h OGTT after a 50 g glucose challenge (Hanson & Kallner 1984). The WHO criteria, using the 75 g OGTT, provide an attractive alternative to other OGTT in pregnancy. Using only two blood samples, it is more acceptable both for the patient and the medical staff.

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Received 6 June 1985
Resubmitted 30 July 1986
Accepted 5 December 1986

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 851–854

Is treatment needed for mild impairment of glucose tolerance in pregnancy? A randomized controlled trial

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Summary. The study was designed to identify those pregnant women who are diagnosed as having gestational diabetes by National Diabetes Data Group (NDDG) criteria, but normal glucose tolerance (NGT) or impaired glucose tolerance (IGT) by the World Health Organization (WHO) criteria, and to test whether treatment changed the perinatal outcome in those with NGT and IGT. The 216 women with an abnormal 100 g oral glucose tolerance test (OGTT) using NDDG criteria were subjected to a 75 g OGTT. Using the WHO criteria, 111 women (51%) had NGT, 98 (45%) had IGT and 7 (3%) had frank diabetes mellitus. Those with NGT and IGT were randomized into control and treatment groups. The perinatal outcome in these two groups was comparable whether the NGT and IGT groups were analysed together or separately except, that in those who were treated for IGT, smaller babies were born one week earlier than in the control group (3407 g *vs* 3110 g, $P<0.01$). This suggests that the WHO criteria can safely replace the 100 g OGTT with substantial savings in manpower, money and patients' time.

In the assessment of abnormal glucose tolerance (GT) in pregnancy, various diagnostic criteria have been used. O'Sullivan's criteria using a 100 g glucose load (O'Sullivan *et al.* 1973) have been in use for many years in North America. Beard *et al.* (1980) advocated a 50 g load whereas the World Health Organization (WHO Expert Committee on Diabetes Mellitus 1980) recommended a 75 g load. Our department has been using the 100 g load and O'Sullivan's criteria as modified by the National Diabetes Data Group (NDDG) (1979) (fasting ≥5·8 mmol/l, 1 h ≥10·6 mmol/l, 2 h ≥9·2 mmol/l and 3 h ≥8·1 mmol/l). It was our clinical impression that the above criteria resulted in the over-diagnosis and overtreatment of those with borderline glucose levels. The recommendations from the National Diabetes Data Group (1979) for the diagnosis of gestational diabetes in the USA was based on the O'Sullivan results. Using these criteria and the WHO recommendation for the diagnosis of 'abnormal glucose tolerance', we have designed this study to assess their applicability in pregnancy, and the need for treatment in those with impaired GT.

Patients and methods

The study involved pregnant women booked at the Tsan Yuk Maternity Hospital, Hong Kong.

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This is a teaching hospital of the Department of Obstetrics & Gynaecology of the University of Hong Kong. The number of women delivered is about 6000 annually and the hospital caters predominantly for a Chinese population of low socio-economic class.

Oral glucose tolerance tests (OGTT) were performed on women with risk factors for gestational glucose intolerance, that is, glycosuria, obesity, clinically large babies, a family history of diabetes mellitus, previous babies over 4 kg, previous unexplained stillbirths, neonatal deaths and recurrent abortions. All the women were given 100 g glucose and venous blood samples were taken fasting and then at 1, 2 and 3 h after glucose ingestion. The National Diabetes Data Group (NDDG) criteria were used to diagnose gestational diabetes. Those who had two or more abnormal values were subjected to a subsequent 75 g OGTT within 2 weeks of diagnosis. Venous blood samples were also taken at fasting, 1, 2 and 3 h after the 75 g glucose drink.

Using the WHO criteria (WHO Expert Committee on Diabetes Mellitus 1980), women with fasting levels of ≥8 mmol/l and/or 2-h levels ≥11 mmol/l during the 75 g OGTT were excluded. The rest of the women were allocated into treatment and control groups alternately, irrespective of whether they had normal GT (NGT) or impaired GT (IGT) according to the WHO criteria. Neither the obstetricians nor the women knew the results of the 75 g OGTT. Those in the treatment group were given a diet containing 30–35 Cal/kg and monitored by blood sugar profiles (pre-prandial, 2 h post-prandial and at 24.00 hours). Apart from routine antenatal visits, the fetus was monitored by monthly ultrasound scans, weekly oestriol assays starting at 32 weeks and weekly cardiotocography commencing at 36 weeks. The women in the control group were not given a diet and did not have sugar profiles.

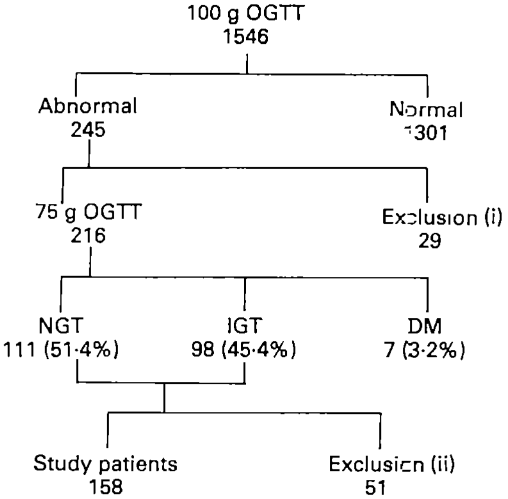

Fig. 1. Results of pregnant women who had both a 100 g and a 75 g oral glucose tolerance test (OGTT) in Tsan Yuk Hospital during the study Exclusions· (i) 29 women who defaulted or were delivered before the 75 g OGTT; (ii) 51 women not managed according to the protocol by individual consultants or delivered within 2 weeks of diagnosis NGT=plasma glucose level at 2 h < 8 mmol/l; IGT=plasma glucose level at 2 h: 8–10·9 mmol/l, fasting <8 mmol/l; DM=plasma glucose level at 2 h ≥11 mmol/l and/or fasting ≥8 mmol/l

The perinatal events recorded included birthweight, birthweight centile for gestational age according to local standards (Ip 1978), Apgar score, duration of first stage, method of delivery, congenital abnormality, birth trauma, respiratory distress syndrome (defined as onset of tachypnoea, subcostal and intercostal retractions within first 4 h of life, progressive increase in oxygen dependency for ≥48 h and typical chest X-ray findings) and hypoglycaemia (blood glucose < 1·1 mmol/l checked by dextrostix every 4 h for 24 h after delivery).

The results of the two groups were compared. We further subdivided the subjects into two subgroups depending on whether the 75 g OGTT was normal (NGT, i.e. 2-h level <8 mmol/l) or impaired (IGT, i.e. 2-h level 8–11 mmol/l) and compared the results between them.

The venous plasma glucose concentration was estimated by the glucose oxidase method using the Beckman Glucose analyser (Beckman Inc., USA) Glycosylated haemoglobin (HbA_1) was measured by agar gel electrophoresis. The normal range for our laboratory is 4–8%.

The results were analysed by the Mann–Whitney *U*-test or the χ^2 test because of the skewed data.

Results

Over a period of 12 months, 1546 pregnant women had a 100 g OGTT and 245 (16%) of them had abnormal results by the NDDG criteria. The subjects excluded and the reasons for exclusion are shown in Fig. 1. Of the 216 women who had a 75 g OGTT, 7 (3%) had diabetes mellitus and were so treated, 98 (45%) had IGT and 111 (51%) had NGT. After all exclusions, 158 subjects were available for analysis.

As shown in Table 1, the women in the control and treatment groups were comparable for age, parity, gestational age at diagnosis and delivery, birthweight, number of large for gestational age (LGA) babies, Apgar score, duration of labour, induction and caesarean section rate.

The number of subjects and the data for each NGT and IGT subgroup are shown in Table 2. There was no difference in any variable between the two subgroups with NGT, whether treatment was given or not. In women with IGT, in the subgroup which received no treatment the mean birthweight was heavier than in the subgroup with treatment (3407 g *vs* 3110 g, $P<0{\cdot}01$) and the mean gestational age at delivery was also greater (39·8 weeks *vs* 38·8 weeks, $P<0{\cdot}001$). The number of babies weighing over 4 kg was also greater in the IGT control group than in the IGT treatment group ($P<0{\cdot}05$). The rest of the data within the IGT group were comparable.

None of the babies suffered from birth trauma or neonatal hypoglycemia. There was no severe asphyxia and no perinatal death with the exception of one baby with multiple congenital malformations.

There were five babies with congenital abnormalities. In the control group, one had multiple abnormalities (absent calvarium, omphalocoele, scoliosis, atelectasis of lung, hyperplasia and hypertrophy of Islets of Langerhans), one had diaphragmatic hernia and one had partial monosomy: 4q syndrome—46XX del(4) (q31.3), ventricular septal defect, cleft lip and palate. In the treatment group, one baby had patent ductus arteriosus and one had hydrocephalus. All but the last were the outcomes of pregnancies diagnosed as IGT using the WHO criteria. The haemoglobin A_1 levels at the time of the IGT diagnosis ranged from 5·9 to 7·2%.

Table 1. Comparison between the control (no treatment) and treatment group

Variable	Control group (no treatment) (n=73)	Treatment group (n=85)
Age (years)	28·9 (4·3)	27·8 (4·6)
Gestation at diagnosis (weeks)		
mean (SD)	31·2 (6·1)	31·7 (5·7)
range	14–38	11–39
Gestation at delivery (weeks)	39·1 (1·9)	38·8 (1·2)
Birthweight (g)	3272 (499)	3196 (387)
No >4 kg	5 (7%)	3 (4%)
No. >90th centile	16 (22%)	15 (18%)
Duration of labour (h)	6·3 (4·1)	7·4 (4·6)
No. with 5-min Apgar score <4	2 (3%)	0 (0%)
Induction rate (%)	16	13
Caesarean section rate (%)	26	27

Results are means (SD) or *n* (%) as appropriate.

Discussion

In this study, the 75 g OGTT was performed only in those women who had an 'abnormal' 100 g OGTT. Ideally the order of the two tests should be randomized in case some women with normal 100 g results have abnormal results with the smaller load. This was not done because the 100 g test was the screening test in the antenatal clinics at the time of study and it was only possible to centralize the 'abnormal 100 g subjects' for a subsequent 75 g test. We believe that the above situation, though not impossible, is highly unlikely and the present study design should not distort the results.

The 100 g OGTT results show that the pregnant women in this population had very mild glucose intolerance. Therefore it is not surprising that the overall perinatal outcome was similar in the treatment and control group.

Neonatal complications and congenital abnormalities were infrequent (5/158) in the combined treatment and no-treatment groups. The congenital abnormalities may have been incidental because the mothers had only mild glucose intolerance and the haemoglobin A_1 levels at diagnosis were normal. The absence of neonatal complications whether treatment was given or not also implied that the mother had mild or no glucose intolerance.

Among those women with an abnormal 100 g OGTT, only 3% had diabetes mellitus using the WHO criteria and these patients were so treated. About 52% of the women had normal glucose tolerance using the WHO criteria and treatment of these women did not offer any clinical benefit. We have demonstrated that it is safe to replace the NDDG test with the WHO test. If this is so, more than half of the pregnant women

Table 2. Comparison of data in the four subgroups

Variable	Normal glucose tolerance Control (1) (*n*=44)	Normal glucose tolerance Treatment (2) (*n*=55)	Impaired glucose tolerance Control (3) (*n*=29)	Impaired glucose tolerance Treatment (4) (*n*=30)
Age (years)	28·9 (4·8)	27·5 (4·8)	28·9 (3·4)	28·4 (4·3)
Gestation at diagnosis (weeks)				
mean (SD)	30·9 (6·3)	32·0 (5·4)	31·6 (5·8)	31·1 (6·3)
range	14–38	16–39	14–38	11–39
Gestation at delivery (weeks)	38·6 (2·3)	38·9 (1·2)	39·8 (0·9)*	38·8 (1·2)*
Birthweight (g)	3182 (509)	3242 (378)	3407 (445)**	3110 (395)**
No. >4 kg	1 (2%)	3 (6%)	4 (14%)***	0 (0%)***
No. >90th centile	9 (21%)	11 (20%)	7 (24%)	4 (13%)
Duration of labour (h)	6·9 (4·5)	7·0 (4·6)	5·3 (3·4)	8·1 (4·5)
No. with 5 min-Apgar scores <4	2 (5%)	0 (0%)	0 (0%)	0 (0%)

Significance of differences between subgroups 3 and 4: *$P<0{\cdot}001$; **$P<0{\cdot}01$; ***$P<0{\cdot}05$.
Results are means (SD) and n(%) as appropriate.

will not be treated as abnormal, and much time, manpower and money can be saved. The women can be spared the unnecessary anxiety of being labelled as diabetic, and they need not suffer the inconvenience and discomfort of diet control, sugar profile and fetal surveillance.

Among those with IGT, women not receiving treatment had slightly heavier babies. This sole difference within the subgroups probably has no clinical significance because there was no increase in the occurrence of induction of labour, birth trauma, asphyxia and hypoglycaemia related to macrosomia. The sample was small, and this needs to be confirmed by larger studies.

Long-term follow-up of women with gestational diabetes mellitus from the Boston Gestational Diabetes Study showed that 50% of them will develop diabetes mellitus in later life (O'Sullivan 1984). It is therefore important to follow up the women of this study to determine how many of those with NGT do develop frank diabetes years later.

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Received 27 June 1986
Accepted 22 February 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp 855–859

Achalasia and pregnancy

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Summary. Forty-one women with achalasia diagnosed between the ages of 18 and 45 years were interviewed and 37 of them who had been married at some time were asked to provide details of their fertility and reproductive histories. Thirty-six agreed to do so and were compared with 36 healthy age-matched women. The mean age at the time of study was 44 and the women had been married, on average, for 21 years. The disease developed at a mean age of 27 years and was diagnosed and treated at a mean age of 32 years. For a mean period of 5 years the disease was untreated. There were no significant differences in the number of conceptions or live births before or after the onset of symptoms or during the period when the disease was untreated. In only three of the 20 women who became pregnant after the onset of disease did symptoms become worse. Achalasia during pregnancy is probably best managed by endoscopic dilatation and there is no reason to consider termination.

Pregnancy have been said to exacerbate symptoms of achalasia and lead to preterm delivery and a poor fetal prognosis. Some centres (Clemendor *et al.* 1969) have consequently advocated termination of pregnancies, but those observations were based on fewer than 20 pregnancies from many different centres. In this study the reproductive histories in women with achalasia have been compared with those in healthy controls.

Patients and methods

Index cases

All women with achalasia which had been treated between 1970 and 1984 in either Cardiff or Nottingham were included in this study, provided they were aged between 18 and 45 years at the time of diagnosis. The study was conducted 18 months after the last patient was treated. Seven of these women were diagnosed before 1970 but had not been successfully treated. A total of 41 women (five from Cardiff, 11 from Nottingham and 25 referred to Nottingham for treatment) were interviewed and 37 who had been married at some time were asked to participate in this study of reproductive performance; 36, including the five from Cardiff, agreed to do so. Each patient provided details of date of birth and age at onset of symptoms, diagnosis and marriage. The dates of birth of their children and the years in which any miscarriages occurred, details of contraceptive practice before and after the onset of symptoms, and symptoms of heartburn and morning sickness during pregnancy were recorded. The relation between onset of symptoms and pregnancy was investigated as was the effect of pregnancy on the symptoms of the disease.

Controls

Married controls were randomly selected from a generally healthy population of administrative

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Table 1. Mean ages of women with achalasia and controls

	Patients (n = 36)		Controls (n = 36)	
	Mean (SD)	Range	Mean (SD)	Range
Age at survey	43·9 (10·9)	25–67	43·9 (10.9)	25–67
Age at onset of symptoms	27·3 (8·6)	10–44		
Age at diagnosis of achalasia	32·3 (9·7)	18–45		
Age at marriage	22·7 (6·6)	17–33	21·5 (3·6)	16–32

Table 2. Number of children born to patients with achalasia and matched controls

	Patient group (n = 36)			Control group (n = 36)				
Time period	Median	Interquartile range	Range	Median	Interquartile range	Range	Wilcoxon matched pairs test	Significance
Before onset of symptoms	1	0–2	0–5	1	0–2	0–6	−0·91	NS
After onset of symptoms	1	0–1	0–4	0	0–2	0–3	−0·31	NS
Before diagnosis	1	0–2	0–5	2	0–3	0–6	−1·3	NS
After diagnosis	0	0–1	0–4	0	0–1	0–3	−1·2	NS
Between onset of symptoms and diagnosis	0	0–0	0–2	0	0–0	0–3	−0·9	NS

and domestic hospital staff. Medical and nursing staff were specifically excluded as controls. Each patient was matched with a control of the same age in years. Subsequent analysis showed that these controls were representative of the general British population. British women born in 1945 have 2·2 children during their reproductive life; the controls used in this study had a mean birth date of 1942 and bore 2·2 children.

Pregnancies

Details of the dates of birth of all children and of miscarriages were collected for each patient and age-matched control and these data were related to the periods before and after both onset of symptoms and time of diagnosis; the time between the onset of symptoms and the date of diagnosis represented a period of untreated disease. For each control, periods of time analogous to those in the patient were compared: i.e. the time before onset of disease, that between onset and diagnosis and that after diagnosis. No data were collected for neonatal health and mortality.

Contraception

Both patients and controls were asked to record their contraceptive practices before and after the onset of symptoms in the patients. Positive responses were recorded where either patient or control had practised any form of contraception for more than 6 months. Both patients and controls were asked to record any episodes of contraceptive pill failure.

Statistical analysis

Paired t-tests were used to compare ages at the time of the survey and marriage. Numbers of children and miscarriages were compared using the non-parametric Wilcoxon pairs signed rank test. The numbers of women who had a miscarriage were compared by χ^2 and 95% confidence limits (Fleiss 1981). Contraceptive practice and

Table 3. Number of miscarriages experienced by women with achalasia and matched controls

	Patient group ($n = 36$)				Control group ($n = 36$)			
	Women with miscarriage	No of miscarriages			Women with miscarriage	No. of miscarriages		
Time period	*n* (95% CI)	Mean (SD)	Range	Median	*n* (95% CI)	Mean (SD)	Range	Median
Before onset of symptoms	7 (3–13)	0·3 (0·7)	0–3	0	5 (2–11)	0·1 (0·3)	0–1	0
After onset of symptoms	3 (1–8)	0·1 (0·3)	0–1	0	2 (0–7)	0·1 (0·7)	0–4	0
Before diagnosis	7 (3–13)	0·3 (0·7)	0–3	0	5 (2–11)	0·1 (0·3)	0–1	0
After diagnosis	3 (1–8)	0·1 (0·3)	0–1	0	2 (0–7)	0·1 (0·7)	0–4	0

CI, Confidence interval.

There was no significant difference between the two groups in the number of women who had a miscarriage (χ^2; 95% confidence limits (Fleiss 1981)) or the number of miscarriages (Wilcoxon matched pairs test).

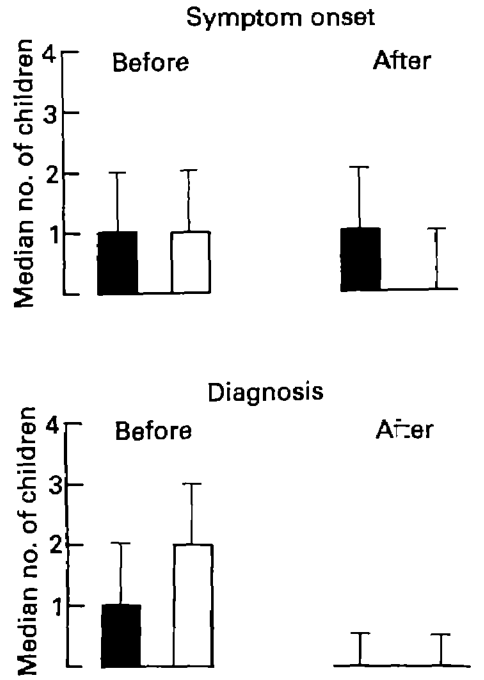

Fig. 1. Median number of live births before and after the onset of symptoms or diagnosis in 36 women with achalasia (■) and in 36 age-matched controls (□). Numbers were obtained by interview in both groups. The vertical bars show the quartile range.

the occurrence of symptoms of heartburn and morning sickness were compared between cases and controls by χ^2 with continuity correction.

Results

Of the 37 married women, 36 were included in the study and their mean age at that time was 43·9 (Table 1). The disease had developed on average 4·6 years after the marriage and was diagnosed 5 years later. There was a period of 16·6 years after onset of symptoms during which the average patient could have become pregnant and for five of these years the disease had been untreated. All patients had been treated at least 18 months before the survey (range 1·5–16·5 years) and only two patients and three controls were married for less than 5 years.

The obstetric history of both patients and controls before the age of onset of symptoms was not significantly different (Tables 2 and 3; Fig. 1). Patients with achalasia had a mean of 1·4 conceptions compared with 1·5 in controls. After the time of onset of symptoms in the index cases both had a mean of 0·9 conceptions. There was no significant difference at any time in the number of live children born or of miscarriages. During the period of untreated disease, patients had a mean of 0·2 children compared with 0·3 in the controls, but this difference was not statistically significant. The median number of children born in both groups during this time was 0. Neither patients nor controls had any miscarriages. The families of both patients and controls showed a skewed distribution and data were compared non-parametrically. There was no evidence that achalasia had any adverse effect on pregnancy or fertility. Contraceptive practice was similar before the onset of symptoms although it was significantly less amongst patients after that (Table 4).

Of the 20 women who became pregnant after the onset of symptoms, 11 noted no change in symptoms, two felt better, three worse and in four the symptoms developed for the first time during pregnancy. There was no evidence that women with achalasia had experienced reflux oesophagitis or morning sickness more frequently than controls (Table 4). One woman with achalasia reported a failure of the contraceptive pill after the onset of her symptoms; no such failure was reported by the healthy controls. No statistical analysis of this difference was

Table 4. Contraceptive practice and symptoms in pregnant women with achalasia and healthy controls

Variable	Patients (n = 36)	Controls (n = 36)	Corrected χ^2	Significance
Use of contraception for >6 months				
Before onset of symptoms	19	12	2·8	NS
After onset of symptoms	8	26	7·1	<0·01
No. of women who became pregnant	31	33		
Experienced severe heartburn	18	15	0·58	NS
Experienced severe morning sickness	15	15	0	NS

possible as no record was made of those patients or controls who used oral contraception as their method of choice.

Discussion

There is little information on pregnancy in women with achalasia and two recent textbooks (de Swiet 1984; Mayberry *et al.* 1986) fail to discuss the problem. Clemendor *et al.* (1969) reviewed the outcome in 10 pregnancies reported by Bloomfield (1963), Karjalainen (1964), Lindert (1956), Roques (1932) and Stroup (1961). All suggested that symptoms worsened and only five of the 10 infants survived. It was suggested that this was due to preterm delivery. Although termination of pregnancy in women with achalasia had previously been advocated, Clemendor *et al.* (1969) felt that pneumatic dilatation of the cardio-oesophageal junction might prevent this necessity. The study reported here is the first to record details of obstetric history before and after the onset of symptoms and to compare this history with a healthy control population. The pattern of the study is similar to that used for a group of patients with Crohn's disease (Mayberry & Weterman 1986).

This study provides no evidence for an adverse effect of achalasia on pregnancy or on fetal outcome. Patients and controls have a similar number of offspring and a similar experience of heartburn and morning sickness. At present there is no indication for the termination of pregnancy in women with achalasia and symptomatic relief can be safely achieved by endoscopic pneumatic dilatation.

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Received 24 July 1986
Accepted 15 January 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 860–863

The predictive value of fetal breathing movements in the diagnosis of preterm labour

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Summary. A real time ultrasound investigation was performed on 64 patients who presented in threatened preterm labour. Fetal breathing movements (FBM) were absent in 17 patients, all of whom were delivered within 56 h. FBM were present in 47 patients of whom five were delivered within 56 h from examination and four of these had spontaneous rupture of membranes and/or chorioamnionitis. In 33 the pregnancy continued for at least 1 week. Two of the fetuses with false negative results showed a distinct breathing pattern different from the rest of the study group. This suggests that pattern recognition of fetal breathing might improve the specificity of this investigation.

Preterm delivery is of serious consequence for the newborn infant with its attendant morbidity and mortality. Primary and secondary prevention of preterm labour are major goals in modern obstetrics. The incidence of preterm birth (MacFarlane & Mugford 1984) has, however, remained static (6–8%) over the past 25 years.

The identification of the patient in progressive preterm labour is mandatory for proper management and optimum fetal surveillance. At least 50% of women who present in preterm labour are either not in labour or stop spontaneously (Anderson 1981). This is compounded by the difficulty encountered in the clinical diagnosis of early labour.

Our study suggests that the presence or absence of fetal breathing movement (FBM) could be used to distinguish between progressive and 'false' preterm labour. The inappropriate use of tocolytics with its potential maternal and fetal side-effects could be avoided and the effectiveness of β-mimetics could be reassessed.

FBM are an integral part of normal fetal physiology from early on in gestation (Trudinger & Knight 1980). Previous studies (Boddy & Dawes 1975) have shown the presence of FBM to be a measure of fetal well-being and that their absence may indicate fetal compromise especially when FBM are used in conjunction with other biophysical variables (Manning *et al.* 1981). These studies have also shown that FBM diminish or cease 24–48 h before active labour commences. Castle & Turnbull (1983) showed a good correlation between the presence or absence of FBM and preterm delivery.

In view of the importance of greater clinical accuracy in the diagnosis of preterm labour we organized a similar study to assess the method.

Patients and methods

The study included 64 patients who presented in threatened preterm labour at between 26 and 37 weeks gestation. Gestation was calculated from the date of the last menstrual period and from an ultrasound scan in early pregnancy when the two estimations were in concordance. If menstrual dates were uncertain, the ultrasound scan was used to calculate gestation. Patients in advanced labour (delivery thought to be imminent) and those considered to be definitely not in labour on

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Table 1. Outcome in patients with no fetal breathing movements

Presentation	No. of patients	Examination–delivery interval (h)
Painful uterine contractions only	5	3–52
Painful uterine contractions + SRM	9	4–32
Painful uterine contractions + APH	3	8–56
Total	17	

SRM, Spontaneous rupture of the membranes; APH, antepartum haemorrhage.

admission to hospital were excluded from the study.

An ultrasound scan was performed on each patient shortly after admission to hospital. A real-time B-mode linear array ultrasound (Diagnostic Sonar System XL Linear Scanner) was employed to detect the presence or absence of FBM with a 3·5 MHz ultrasound probe. A continuous ultrasound scan was performed for 45 min if FBM were absent but sustained FBM of at least 20 s duration with a breath to breath interval of <6 s was used to indicate their presence.

The fetus was outlined in a sagittal plane and the fetal thorax, heart, diaphragm and abdomen were displayed. FBM were identified as paradoxical movements of the fetal thorax and abdomen with downwards movement of the diaphragm and abdominal contents.

Passive movement of the fetus due to maternal respiration or pulsation of the maternal aorta were carefully excluded. Fetal gross movements were considered a period of apnoea as demonstration of FBM was impossible.

The patients were divided into two groups according to the presence or absence of FBM. Each of the groups was subdivided into three subgroups based on defined criteria at presentation: (a) painful uterine contractions only; (b) painful uterine contractions with spontaneous rupture of membranes (SRM); (c) painful uterine contractions with antepartum haemorrhage (APH).

The cervical dilatation and effacement was noted and recorded on admission.

The fetal breathing pattern and other biophysical variables (biophysical profile) were observed, but the results are not included in this paper.

Results

By using real-time ultrasound, FBM were clearly seen and easily distinguished from other fetal movements. The 64 women had 75 ultrasound examinations.

When FBM were absent, preterm delivery was anticipated. The diagnostic accuracy was good as all 17 patients without FBM were delivered within 56 h (range 3–56 h). No differences in time-interval were noted in the three subgroups (Table 1). Two fetal deaths occurred in this group.

FBM were present in 47 patients of whom 42 (89%) continued the pregnancy for at least 56 h and 70% continued the pregnancy for at least 1 week (Table 2).

These findings were assessed in the different subgroups. Patients presenting with either SRM or APH along with contractions represent a special category. Epidemiological studies show that most patients with SRM are delivered within 72 h from membrane rupture.

Seven patients presented with SRM and FBM of whom two were delivered within 56 h, but only one continued the pregnancy for more than 1 week. Traditional assessment methods by ster-

Table 2. Outcome in patients with fetal breathing movements present

Presentation	Examination–delivery interval <56 h	56 h–1 week	>1 week	Total
Painful uterine contractions	3	1	27	31
Painful uterine contractions + SRM	2	4	1	7
Painful uterine contractions + APH	0	4	5	9
Total	5	9	33	47

SRM, Spontaneous rupture of the membranes; APH, antepartum haemorrhage ile speculum examination did not aid the diagnosis of imminent labour. The cervix was closed in all patients on admission.

Nine patients presented with APH associated with painful uterine activity but neither the bleeding nor the fetal condition was sufficient to warrant immediate delivery. None was delivered within 56 h, but four were delivered within 1 week.

Thirty-one patients presented with painful uterine contractions; three of them were delivered within 48 h and four others were delivered within a week. In each of these four patients the cervix was found to be fully effaced and more than 2 cm dilated (range 2–5 cm). Where the pregnancy continued the cervix was uneffaced and not dilated.

The false negative rate requires further consideration. FBM are considered to diminish or cease 24–48 h before the establishment of active labour. Of 47 patients only five were delivered within 56 h of the examination.

In two of these patients rupture of membranes was a complicating factor, one of whom was found to have a severe chorioamnionitis but histopathology was not available for the other. The other three patients had intact membranes and two had severe chorioamnionitis associated with an unusual fetal breathing pattern.

Of the nine patients who were delivered within 1 week, four had been admitted with APH and sustained a further haemorrhage requiring delivery. Three patients with SRM progressed to delivery, infection being diagnosed in two on histological and bacteriological examination. One patient with SRM subsequently had a significant APH at 36 weeks gestation that required delivery. In one patient artificial rupture of membranes (ARM) was performed for maternal distress but she subsequently required stimulation with oxytocics.

No false negative results were obtained when FBM were absent. When FBM were present, 90% continued their pregnancy for more than 56 h. False negative results were associated with chorioamnionitis with or without SRM. Of the patients admitted with intact membranes and FBM, 87% went to term and another scan 56 h after admission did not provide any further information. Patients presenting with other complicating factors such as SRM or APH show a different pattern as was expected and repeat ultrasound scan examinations on an in-patient basis might aid in establishing the accurate timing of delivery.

Discussion

This study shows a strong relation between the presence or absence of FBM and preterm labour.

We confirmed the findings of Castle & Turnbull (1983) and demonstrated the clinical value of the method.

FBM have a diurnal variation and are episodic in nature (Campbell *et al.* 1980). Long periods of apnoea are considered normal and a long examination period is often necessary to reach a diagnosis. This makes the method less appealing for use in clinical practice.

The observation that maternal glucose concentration affects the breathing of the fetus is interesting (Lewis & Trudinger 1978). FBM have been shown to increase significantly after a meal or after a maternal oral or intravenous glucose load.

The maximal increase in FBM is seen 1 h after the peak in maternal glucose concentration (Natale *et al.* 1978), but a rise is seen 15 min after an oral glucose load. This would shorten the examination time considerably and 15 min of scanning would be adequate 30 min after an oral glucose load.

Fetal breathing pattern changes with gestation (Trudinger & Knight 1980). It is usually described as rapid and irregular in character mimicking the variability seen in a normal fetal cardiotocograph.

In two of the patients with false negative results the breathing pattern was distinctive. The episode of breathing was regular, resembling a sine wave with a greater breath amplitude and an increased breath to breath interval. Both these pregnancies showed severe chorioamnionitis on histopathological examination.

As the breathing pattern was not analysed specifically, these have to be regarded as isolated findings but suggest that pattern recognition might improve the specificity of the method.

The absence of FBM is associated with fetal compromise but because FBM are episodic, their absence is not reliable on its own. Two fetal deaths occurred in the group where no FBM were detected, and in both these fetuses a low biophysical profile score was obtained. Persistent APH was a complicating factor in one pregnancy. This fetus at 30 weeks gestation showed no gross fetal movements or fetal tone. The other pregnancy was complicated by a cord prolapse. This fetus showed no fetal gross movements over the observation time.

It is our belief that investigation of FBM is valuable in the management of preterm labour. The detection of FBM in patients with uterine activity but no other complicating factors would minimize the stay in hospital and unnecessary medication could be avoided. Identification of the fetus at risk both for preterm birth and fetal compromise allows better fetal surveillance during labour and improves neonatal outcome.

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Received 29 September 1986
Accepted 27 October 1986

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 864–869

Prostaglandin E production by amniotic cells in relation to term and preterm labour

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Summary. The rate of prostaglandin E (PGE) production was measured in collagenase-dispersed amniotic cells obtained from 14 women after spontaneous labour at term—seven after spontaneous preterm labour, nine after delivery by elective caesarean section at term and six after induction of labour at term. Cells were incubated with and without arachidonic acid and PGE was estimated by specific radioimmunoassay. Basal PGE output (pmol/10^6 cells per 3 h) was highest in the spontaneous labour group, 27·5 (SEM 5·5) and lowest in the preterm labour group, 4 (SEM 1·2) ($P<0{\cdot}001$). Values in the elective section and induction groups were 13·6 (SEM 2·7) and 10 (SEM 3·1), respectively; these values were significantly higher than in the preterm labour group and the values after induction were significantly lower than after spontaneous labour. Addition of arachidonic acid resulted in a significant increase in PGE output in all groups, but the values after preterm labour remained significantly lower than those of any group at term. These data indicate that towards term there is a maturation in the PG synthetase activity of the amnion and that PGE output in this tissue is increased in spontaneous labour.

The endocrine or paracrine factors responsible for the initiation of human parturition remain unknown, but it is likely that prostaglandins (PG) play a prominent role. The amniotic epithelium is an important intrauterine site of prostaglandin production, especially of PGE (Kinoshita *et al.* 1977; Mitchell *et al.* 1978). Since PGE binds with high affinity to specific receptors in the uterus (Wakeling & Wyngarden 1974; Adelantado *et al.* 1985) and can stimulate myometrial contractility and cervical ripening (Karim *et al.* 1970; MacKenzie & Embrey 1977), production of PGE by amnion cells seems likely to play an important physiological role in controlling the onset of human labour.

The PGE production rate of amnion has been measured *in vitro* in tissues obtained at term before and after the spontaneous onset of labour and, although some controversy persists, amniotic PGE output appears to be increased in samples obtained after the onset of labour (Olson *et al.* 1983; Manzai & Liggins 1984). The mechanism bringing about this increase remains unexplained. Since little has been published about amniotic PGE production in 'uncomplicated' preterm labour, it is important to discover whether or not it is initiated by the same control mechanism as spontaneous labour at term.

The purpose of this study was to compare the endogenous and arachidonic acid-stimulated

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PGE production rate in amniotic cells obtained from patients delivered before or after spontaneous or induced labour at term and after preterm labour.

Patients and methods

Amnion was obtained after spontaneous labour at term in 14 women; at elective caesarean section at term in nine women; after induced labour at term in six; and after preterm labour in seven. All women were delivered of healthy singleton infants. Sections were performed because of previous section or malpresentation. Labour was induced by intravaginal administration of PGE_2 (2·5–5 mg) followed by amniotomy after 3 h. None of the women in preterm labour received tocolytic drugs. Further clinical details are summarized in Table 1.

Preparation of cell suspensions

The amnion was rinsed in ice-cold Krebs–Henseleit solution containing 10 mM Hepes, pH 7·4, and 5 mM glucose (Krebs solution). Slices (0·5 mm) of amnion were transferred to flasks containing 0·1% collagenase (Sigma type I) and 0·05% hyaluronidase (Boehinger, Mannheim) in Krebs solution without calcium or magnesium, pregassed with 95% O_2–5% CO_2. The flasks were incubated at 37°C for 1 h and the contents of the flasks were then filtered through a 170 μm nylon mesh. The resulting cell suspension was washed three times in Krebs solution and samples were taken for estimation of cell viability (by phase contrast and/or trypan blue staining) and concentration. Cell suspensions of less than 60% viability were discarded. Dispersed cell yields averaged 0·6 (SEM 0·01) × 10^6 cells/g tissue (n=30).

Incubations

Unless otherwise specified, the cells were incubated in polypropylene tubes containing 10^5 cells/ml at 37°C under air in a humidified atmosphere. Cells were incubated alone and in the presence of 10 μM sodium arachidonate (Sigma). At appropriate times the tubes were cooled and centrifuged at 100 *g* for 10 min and the supernatants were stored at −20°C. Control tubes contained cells boiled for 5 min.

Prostaglandin E estimations

PGE was measured by radioimmunoassay (Gibson *et al.* 1985). The antiserum was kindly donated by Dr S. P. Brennecke and cross-reacted with other prostanoids (Upjohn, Kalamazoo) as follows: PGE_2 100%, PGE_1 100%, PGA 8%, 6-oxo-PGE 7%, 13,14-dihydro-PGE_1 6%, PGA_2 3%, $PGF_{2\alpha}$ 2%, 13,14-dihydro-PGE_2 and $PGF_{1\alpha}$ 1%. The results are expressed as PGE as the antiserum does not distinguish between PGE_1 and PGE_2.

Intra- and inter-assay coefficients of variation were 9·6% and 13·7% respectively.

Oxygen uptake and lactate estimations

Oxygen consumption was estimated at 37°C in suspensions containing 0·5 × 10^6 cells/ml in Krebs solution with the use of a model 5331 oxygen probe (Yellow Spring Instrument Co , Ohio).

Aliquots (1 ml) of cell suspensions were mixed with 0·4 ml 3 N perchloric acid and were centrifuged at 8000 *g* for 5 min; lactate was measured in the supernatant by the method of Gutman & Wahlefeld (1974).

Table 1. Clinical data of patients

Patient group	*n*	Maternal age (years)	Gestational age (weeks)	Parity	Birthweight (g)
Spontaneous labour	14	25 (2)	39 (0·4)	0·4 (0·2)	3289 (212)
Preterm labour	7	24 (2)	31 (1·0)	0·9 (0·4)	1619 (239)
Elective caesarean section	9	31 (2)	38 (0·2)	0·3 (0·2)	3263 (96)
Induced labour	6	30 (2)	40 (0·5)	0·8 (0·3)	3383 (226)

Results are means (SEM)

Statistics

Statistical differences were assessed by the Kruskal–Wallis and Mann–Whitney tests.

Results

Oxygen uptake and lactate production

The mean oxygen uptake in three different cell preparations was 0·15 (SD 0·07) μmol/10^6 cells per h. The rate of oxygen uptake was similar in the presence or absence of glucose (5 mM) and/or insulin (Novo, 40 mU/ml). The basal lactate production rate was 0·06 (SD 0·001) μmol/10^6 cells per h and increased to 1·13 (SD 0·02) μmol/10^6 cells per h in the presence of added glucose (5 mM).

Endogenous PGE production

As shown in Fig. 1, under our incubation conditions, amniotic cells obtained before and after labour produced PGE at a constant rate for about 3–4 h; thereafter, PGE levels remained stable. PGE production was inhibited by indomethacin and was abolished by boiling the cells. Figure 2 shows the endogenous PGE production rate in the different groups. Mean (SEM) values (pmol/10^6cells per 3 h) ranged from 27·5 (5·5) in term labour to 4 (1·2) in preterm labour, with intermediate values at elective caesarean section and after induced labour. Overall (Kruskal–Wallis test) the differences were statistically significant (P<0·001). Comparisons between groups (Mann–Whitney test) revealed that the values in preterm labour were significantly lower than in any of the other groups (P<0·05–0·002). At term, the values after spontaneous labour were significantly higher than after induced labour (P=0·02); the values at elective caesarean section were lower than after spontaneous labour and higher than after induced labour, but these differences were not statistically significant.

PGE production in the presence of arachidonic acid

With added arachidonic acid the PGE production rate increased significantly in all groups (P<0·001) and, as shown in Fig. 3, a similar pattern to that described in Fig. 2 was obtained. Again, the largest difference was obtained between spontaneous term and preterm labour [46·6 (SEM 5·8) compared with 22·4 (SEM 3·6)

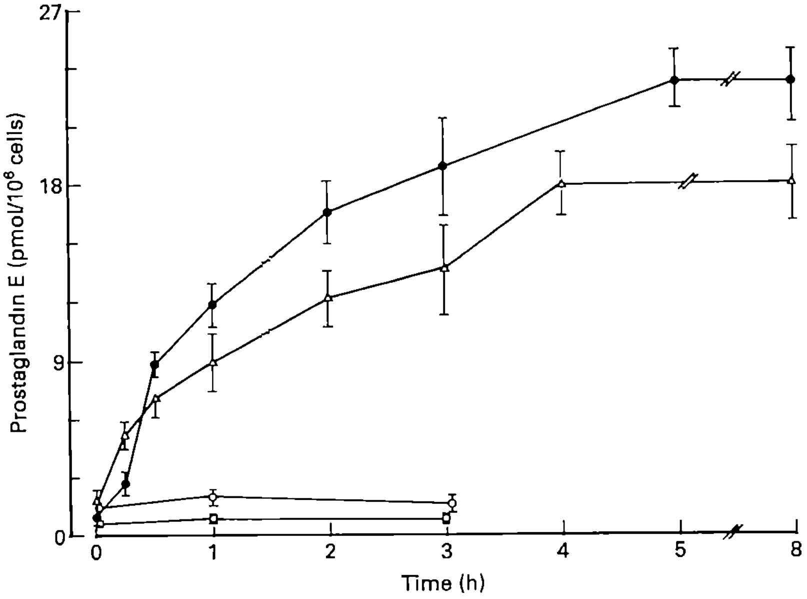

Fig. 1. Prostaglandin E production by dispersed amniotic cells. (●—●) Spontaneous labour, (△—△) elective caesarean section; (○—○) indomethacin; (□—□) boiled cells. The bars represent the standard deviation of triplicate estimations. Indomethacin was used at 10 μM.

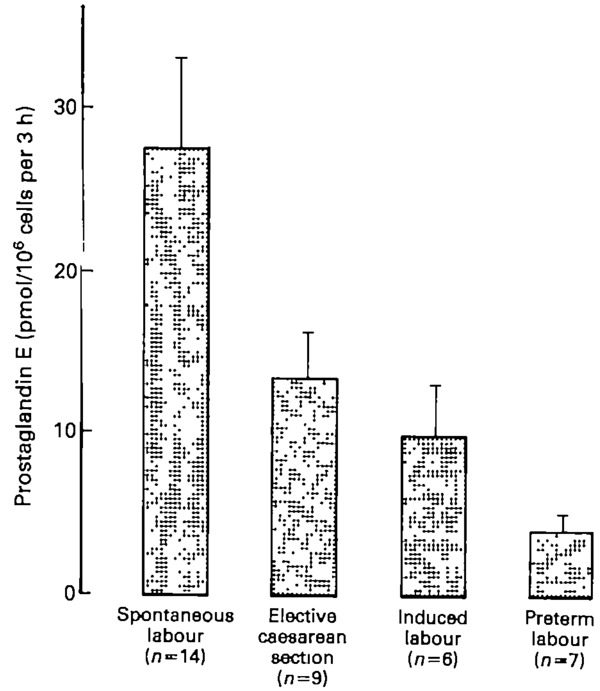

Fig. 2. Prostaglandin E output by dispersed amniotic cells in relation to the mode of onset of labour The vertical bars represent SEM.

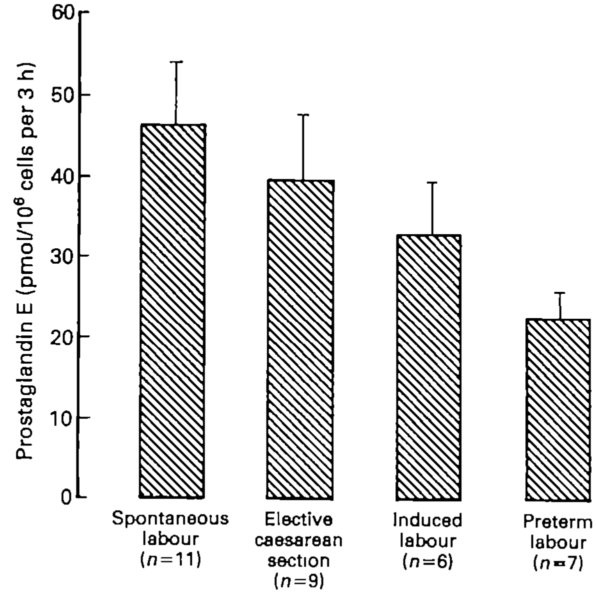

Fig. 3. Prostaglandin E output by dispersed amniotic cells in relation to the mode of onset of labour Incubations were carried out in the presence of 10 μM arachidonic acid as described in the text. The vertical bars represent SEM

pmol/10^6 cells per 3 h, respectively]. The overall differences were significant ($P<0{\cdot}001$) and analysis between groups revealed that the values in preterm labour were significantly lower ($P<0{\cdot}05$–$0{\cdot}002$) than any of the other groups at term. Moreover, the difference between term spontaneous labour and elective section or induced labour were not statistically significant.

Discussion

Amniotic epithelium cells are arranged in a monolayer and can be dispersed by gentle shaking in the presence of collagenase-hyaluronidase. The high glycolytic rate of these cells resembles that of other intrauterine tissues such as the placenta and decidua (Sakurai *et al.* 1969; López Bernal 1984) and their low oxygen requirement make them suitable for in-vitro work. Our findings confirm that dispersed amniotic cells produce PGE and the production rates are very similar to those reported by Olson *et al.* (1983) and Manzai & Liggins (1984). These workers found a significantly higher rate of amniotic PGE production after spontaneous labour at term than at elective caesarean section, and our data tend to support their findings, although in our series there was considerable overlap between the two groups and the difference was not significant. Other workers have found no statistically significant difference in amniotic PGE production rates before and after labour at term (Mitchell *et al.* 1978; Satoh *et al.* 1981). Nevertheless, the relatively low level of PGE production in amniotic cells from our women whose labour was induced with PGE_2 supports the concept that spontaneous parturition is associated with an activation of PG production in this tissue, independent of the process of labour itself. However, a possible inhibitory effect of the administered PGE_2 pessaries on amniotic PG synthetase activity in the induced labour group cannot be ruled out.

A likely explanation for increased amniotic PG production in spontaneous labour is an increased mobilization of arachidonic acid from tissue phospholipids (Okita *et al.* 1982). Addition of arachidonic acid to our incubations simulated the increased precursor availability and resulted in a 2–3 fold increase in PGE output, confirming that substrate availability is an important determinant of the rate of PGE synthesis. Okazaki *et al.* (1981) have reported an actual increase in the conversion rate of radiolabelled arachidonic acid into PGE in homogenates of amnion obtained after spontaneous labour compared with tissues obtained at elective caesarean section; but recent studies (Dimov *et al.* 1983) suggest the metabolism of radiolabelled arachidonic acid in tissue homogenates can only be interpreted in a semi-quantitative way.

This study has revealed that in amnion cells obtained after preterm labour, the PGE production rate is low compared with that in amnion from any group at term. The difference was significant both in the presence and absence of added arachidonic acid and suggests that, towards term, PG synthetase activity in the amnion is increasing. A similar increase has been described (Risbridger *et al.* 1985) in collagenase-dispersed trophoblastic cells from pregnant sheep. Previous studies in human pregnancy have suggested that spontaneous preterm labour may be associated with relatively low PG production (TambyRaja *et al.* 1977; Sellers *et al.* 1981). These findings raise the possibility that the mechanism which initiates preterm labour in the absence of obvious pregnancy complications may differ to some extent from that which regulates the onset of labour at term.

While the mechanism controlling the increased PG production with human parturition remains unexplained, this study suggests that towards term prostaglandin synthetasing activity is increasing in human amnion, and that availability of free arachidonic acid is an important determinant of amniotic cell PGE production both before and after 37 weeks gestation. Further work is in progress to establish whether the increased intrauterine PG release, which is associated with human parturition and reflected in the rate of amniotic PGE production *in vitro*, results from activation of PG synthesis, the withdrawal of inhibitors, or both.

Acknowledgment

This study was supported by Action Research for the Crippled Child.

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Received 26 August 1986
Accepted 1 December 1986

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 870–872

Postpartum pelvic arthropathy with unusual features

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Summary. Eleven patients seen in Malawi are described with a syndrome of postpartum pelvic arthropathy. They complained of severe pain mainly located in the symphysis pubis and all were unable to walk. The following unusual features were noted: the absence of obstetric trauma, a symptom-free interval between the delivery and the onset of the syndrome, the absence of gross widening of the symphysis pubis and the lack of abnormal mobility in the same joint. It is speculated that the syndrome described is not caused by rupture of the symphysis or softening under the influence of hormones but by swelling inside the intact fibrous confines of the joint.

Syndromes of pain in the pelvic girdle associated with pregnancy are commonly referred to as pelvic (osteo)arthropathy or (spontaneous) symphysiolysis. Usually two different syndromes are described. In the first, abnormal mobility develops in the pelvic joints, which causes pain and sometimes a waddling gait either during pregnancy or in the puerperium. The second syndrome develops after a difficult vaginal delivery and is characterized by signs of a traumatic rupture of the symphysis pubis. In Malawi I observed patients whose symptoms did not fit either pattern. They would typically become unable to stand or walk 1 or 2 days after a normal delivery because of pain in the area of the symphysis pubis. Direct palpation of the symphysis and axial pressure applied over both trochanters was extremely painful. There was no swelling or bruising over the symphysis and abnormal mobility or widening of the joint was in doubt. The symptoms subsided in a week or two with rest and simple analgesics. Because this syndrome seemed different from those usually described, the following prospective study was done.

Patients and methods

The study was done in the maternity department of the Queen Elizabeth Central Hospital, Blantyre, Malawi between 1 April and 31 December 1984. During this period between 8000 and 9000 women were delivered in the department, including unselected cases from the city as well as patients referred from a wide surrounding area. The overwhelming majority were of African origin and none of the patients in the study was non-African.

I personally interviewed and examined, according to a standard protocol, all patients presenting with severe pain in the pelvic girdle after delivery. Only patients with all of the following features were admitted to the study: pain and tenderness over the symphysis pubis, pain in the symphysis pubis on axial pressure and inability to walk. On average, patients were seen 98 h after delivery (range 53–138 h).

Eleven patients were studied. The mean age of the nine patients whose age was known or estimated was 30 years (range 21–34); for two patients the age was not recorded. The mean parity (including the last delivery) was 6 (range 2–11). Nine women were delivered at term, one at 33 weeks and one at 43 weeks. Nine had a spontaneous vertex delivery, eight of their babies were alive and well. One had a macerated stillbirth at 33 weeks, weighing 2100 g. One patient, whose baby weighed 3860 g at 43 weeks gestation, had an uncomplicated caesarean section for delay in the second stage. One patient gave birth to twins: the first twin was born spontaneously in vertex presentation, weighed 2660 g

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and was well. The second twin was born by an assisted breech delivery, weighed 2700 g and was stillborn for an unknown reason.

The mean birthweight of the 10 singleton babies was 3100 g (range 2100–3860).

No patient suffered major soft tissue injuries. Nine patients had clinical evidence of uterine infection and most of them received an antibiotic.

Results

All patients had a symptom-free interval after delivery, lasting on average approximately 30 h (range 8–60). Nine described the onset of the pain as gradual and in the remaining two the mode of onset was uncertain. Eight noticed the pain first while they were lying down, one when walking and two were uncertain about their activity at the time of onset. Only one patient had had mild pain in the pelvic girdle during pregnancy. One patient reported that she had had a similar syndrome after the previous delivery.

All patients localized the pain in the area of the symphysis pubis, one also complained of pain in the back, one about pain in the buttocks and one about pain in the groins and 'inside'. The main area of tenderness was over the symphysis pubis but it often extended over a few centimetres along the superior or inferior pubic rami, both on external and internal palpation. Only in one patient could some swelling be detected in front of the symphysis. Two patients were tender on palpation over the sacroiliac joints, no tenderness was demonstrated in the others. The distance of the pubic bones was difficult to assess clinically because of the severe pain on palpation. However, in no patient was a very wide gap noted. Seven patients had X-rays of the pelvis. The width of the gap varied from 6 to 18 mm with an average of 11 mm.

The mobility in the symphysis was also hard to assess clinically due to the severe pain. However, seven patients felt abnormal movement in the joint whereas four noted none. The examiner noted only slight movement in two patients, in one under anaesthesia which was needed for the exploration of the uterus due to secondary postpartum haemorrhage. In the other nine women no movement could be elicited by pulling on or flexing one leg. Two patients were X-rayed with traction on one leg and no movement in the symphysis could be demonstrated. X-rays with abduction and moderate flexion in four other patients also failed to demonstrate movement. Treatment consisted of rest in bed with a fracture board under the mattress and the administration of simple analgesics like aspirin or paracetamol. The mean stay in hospital was 12 days (range 7–18). All patients went home walking.

Discussion

An important feature in these patients is the absence of trauma during delivery. Their babies were not unusually big, the average birthweight being similar to the average of 3150 g recorded in the same hospital for 104 healthy Malawian infants (Gerritsen & Driessen 1983). Callahan (1953) and Hyslop (1964) who described patients with a similar syndrome, both considered injury during delivery to be important

Another unusual feature is the symptom-free interval after delivery. This is not mentioned in a number of standard textbooks (Benson 1984; Dewhurst 1981; Donald 1969; Kloosterman 1973; Myerscough 1977). It was described in one North African patient by Lacomme (1960) and referred to by Prokop'ev & Prokop'eva (1980). Unfortunately, the latter describe none of their patients in detail. Hyslop (1964), who described 18 patients with separation of the symphysis pubis from Nairobi, noted that the pain started during or almost immediately after delivery.

The third unusual feature is that we were unable to demonstrate abnormal mobility in the symphysis. Admittedly, some of our patients were aware of movement in the joint but this discrepancy can be explained by assuming that normal movement was excessively painful.

It is difficult to define the degree of abnormality of the recorded separation of the pubic bones. The average of 11 mm in our patients is more than the average of 5 mm assumed to be normal by Myerscough (1977), but in no patient was it more than 2 cm, which Benson (1984) considers to be the upper limit of normal separation in pregnancy.

The incidence of uterine infection seems rather high. Unfortunately this aspect was not documented in detail so its relevance is hard to assess. Also the incidence of uterine infection in other patients is unknown as most leave the department within 24 h after delivery.

The aetiology of the syndrome is a mystery to me. The features of our patients seem incompatible with a traumatic rupture of the symphysis. If abnormal softening under the influence of hormones were the cause, one would expect more evidence of excessive mobility in the joint and perhaps also a greater degree of separation of the pubic bones. I suggest that swelling and an increase in pressure within the fibrous confines of the joint are a more likely cause. Swelling would take time to develop and explain the symptom-free interval as well as the gradual onset of the pain. Swelling would tighten intact fibrous ligaments and movement in the joint would tend to be restricted. Swelling in the joint would force the pubic bones apart but separation would be restricted by intact ligaments and thus be moderate. The present study offers no firm evidence as to why swelling would occur in these women.

Finally, it is hard to believe this syndrome occurs only in Malawi. Perhaps some cases recorded elsewhere were wrongly ascribed to hormonal softening or traumatic rupture.

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Received 20 May 1986
Accepted 24 September 1986

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 873–879

Apgar score, meconium and acidaemia at birth in small-for-gestational age infants born at term, and their relation to neonatal neurological morbidity

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Summary, Neonatal neurological morbidity was studied in relation to Apgar score, meconium stained amniotic fluid and acidaemia at birth in 247 small-for-gestational age (SGA) maturely born infants. SGA infants, and especially the severely SGA infants and those born abdominally, showed higher rates of neurological morbidity, acidaemia and meconium stained amniotic fluid than appropriate-for-gestational age (AGA) controls. The examined indicators of asphyxia at birth showed slightly higher correlation coefficients with the 'neonatal neurological optimality score' (NNOS) in SGA, than in AGA term infants, but the percentage of explained variance was low, except in the 23 infants born abdominally. In this group poor neurological outcome was restricted to the 14 infants who showed signs of fetal hypoxaemia diagnosed by decelerative fetal heart rate (FHR) patterns. In 11 of them, FHR decelerations occurred antepartum. These FHR abnormalities appear to be better predictors for the neonatal neurological outcome than indicators of asphyxia at birth.

Mature small-for-gestational age (SGA) infants show an increased frequency of neurological abnormalities not only in the neonatal period (Huisjes *et al.* 1980) but also at a later age (Fitzhardinge & Stevens 1972; Neligan *et al.* 1976). Various suggestions have been made about the aetiological background of these long-term sequelae. On the one hand a relation between late neurological impairment and the severity of intrauterine growth delay has been demonstrated (Neligan *et al.* 1976), reflecting perhaps the reduction of brain weight (Larroche & Korn 1977) and brain cell number (Winick & Rosso 1969). On the other hand it has been suggested that the increased incidence of asphyxia (Low *et al.* 1978) might contribute to the incidence and severity of late handicap in these mature SGA infants (Dweck *et al.* 1974).

To make rational decisions about the type of intervention in pregnancies complicated by poor intrauterine growth it is important to answer the question, as to what contribution the associated hazard of intrapartum hypoxaemia/acidaemia makes to the occurrence and severity of neurological handicap and what would be the 'residuum of handicap' when hypoxic insults are prevented (Tayler 1984). In an earlier study in appropriate-for-gestational age (AGA) full-term infants we found a very low correlation between indices of asphyxia (such as low Apgar scores, umbilical acidaemia and meconium

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stained amniotic fluid) and the neonatal neurological condition (Dijxhoorn *et al* 1986). However, in a combined group of term and preterm SGA infants acidaemia nearly doubled the rate of neonatal neurological abnormality (Huisjes *et al.* 1980). No studies have as yet been published on the relation between Apgar scores alone or in combination with umbilical cord acid-base values on the one hand and neonatal neurology on the other in SGA infants born at term. Such studies would nevertheless be of interest since the added impact of prematurity on the central nervous system is excluded.

In the present study the relation between indices of asphyxia at birth and the neonatal neurological condition were investigated in severely and moderately SGA infants born at term, delivered vaginally or by caesarean section.

The data are compared with those of earlier studies on AGA term infants (Dijxhoorn *et al.* 1985, 1986).

Patients and methods

Subjects were selected from the data base of the Groningen Perinatal Project, containing pre- and perinatal data on 3162 children from consecutive singleton pregnancies, all surviving the neonatal period. Of these infants, 2991 were born after 37 completed weeks gestation and 374 (12·5%) of them were below the 10th centile for birthweight according to the Amsterdam growth charts (Kloosterman 1970). In 247 of these 374 infants umbilical artery pH(pH_{ua}) values were available, 23 of them were born by caesarean section and 224 vaginally. In the latter group 178 had a birthweight between the 2·3 and 10th centile (moderate SGA) and 46 below the 2·3 centile (severe SGA). A complete blood gas analysis, including $P\text{CO}_2$ and base excess (BE) of blood from the umbilical artery and maternal vein, was available in 130 of the SGA infants (53%).

Two control groups of AGA term infants were selected from the Perinatal Project cohort. One included 805 vaginally born infants selected only because a complete acid-base status of mother and infant taken directly after birth was available. This group was representative of the total group of AGA term infants, as has been described previously (Dijxhoorn *et al.* 1985). The second control group consisted of 82 infants born by section with known pH_{ua} values.

The newborn infants were assessed by Apgar scores at 1 and 3 min (data available for 1129 of 1134 infants) and by taking blood from the umbilical artery and from the maternal cubital vein for blood gas analysis directly after birth. The presence or absence of meconium in the amniotic fluid at the time of rupture of the membranes was noted.

The results of a standardized neurological examination (Prechtl 1977) were expressed in a neurological classification (normal, suspect or abnormal) and in a neonatal neurological optimality score (NNOS; range 0–60) (Touwen *et al.* 1980; Dijxhoorn *et al.* 1985).

Statistical analysis

The Student's *t*-test, the Mann–Whitney *U*-test, the χ^2 test (Tables 1 and 4) and the analysis of variance (for mean pH_{ua} values) or the Kruskal–Wallis test (for median 1-min Apgar scores; Table 2) were used. Multiple regression analysis was used to examine the effects of acid-base variables, Apgar scores, and meconium on the NNOS as the dependant variable (Table 3). The squared multiple correlation coefficient (R^2) indicates the proportion of variance in NNOS explained by the indicators of asphyxia.

Results

SGA infants scored less than AGA controls on all but one of the indices of neonatal morbidity (neonatal neurological diagnosis, optimality score, pH_{ua} and ΔpH_{m-ua}). For the Apgar scores no significant differences were found. Severely SGA infants did worse than moderately SGA infants. Both in the study and control groups the poorest outcome was found in infants born by caesarean section (Table 1).

In the vaginally-born infants, both the SGA and the AGA, the median values of 1-min Apgar scores, but not the mean pH_{ua}, declined with the impairment in neurological diagnostic classification (normal, suspect, abnormal). Both the 1-min Apgar score and the pH_{ua} declined in the two categories of infants born abdominally (Table 2), but the decrease was only significant for the pH_{ua}.

The indices of asphyxia contributed more to the explanation of variance in NNOS in the SGA infants than in the control group of AGA infants (Table 3). However, the percentage of explained variance was low in all subgroups,

Table 1. Indices of neonatal morbidity in various study groups of infants born at term according to birthweight centiles (<2·3 centile = severe SGA; 2·3–10th centile = moderate SGA; >10th centile = AGA) by mode of delivery

	Vaginal delivery					
	Small-for-gestation (SGA)				Caesarean section	
Neonatal outcome	Severe ($n = 46$)	Moderate ($n = 178$)	Total ($n = 224$)	AGA ($n = 805$)	SGA ($n = 23$)	AGA ($n = 82$)
Neurological condition						
Normal (%)	40	68	62	77	48	70
Suspect (%)	36 —**—	26	28 —*—	19	35 —*—	23
Abnormal (%)	24	6	10	4	17	7
NNOS						
Median	52·9 —**—	55·2	54·8 —*—	55·2	53·5	54·5
Interquartile range	49–55	53–57	54–57	53–57	49–56	51–57
1-min Apgar score						
Median	8·4	8·7	8·7	8·7	7·8	7·8
Percentage <7	15	7	9	8	29	32
pH_{ua} mean (SD)	7·17 (0·09) —*—	7·19 (0·10)	7·19 (0·10) —**—	7·22 (0·09)	7·18 (0·09)	7·19 (0·10)
ΔpH_{m-ua} mean (SD)	0·16 (0·10)	0·14 (0·10)	0·15 (0·10) —**—	0·12 (0·08)	0·15 (0·10)	0·15 (0·09)

NNOS, Neonatal neurological optimality score (Touwen *et al*. 1980).
SGA, Small-for-gestational age; AGA, appropriate-for-gestational age
* P<0·05; ** P<0·01.

Table 2. Median 1-min Apgar score and mean pH by neonatal neurological classification in appropriate-for-gestational age (AGA) and small-for-gestational age (SGA) term infants born vaginally (VD) or by caesarean section (CS)

			Neonatal neurological diagnostic category						
	Groups	(n)	Normal	(n)	Suspect	(n)	Abnormal	(n)	
1-min Apgar score	AGA VD	(803)	8·7	(617)	8·4	(156)	8·4	(30)	P<0.01
	SGA VD	(224)	8·7	(139)	8·5	(63)	8·1	(22)	P<0.005
	AGA CS	(79)	8·0	(54)	7·0	(19)	6·0	(6)	NS
	SGA CS	(23)	8·5	(11)	7·0	(8)	5·5	(4)	NS
pH_{ua}	AGA VD	(805)	7·22	(619)	7·20	(156)	7·22	(30)	P<0.025
	SGA VD	(224)	7·19	(139)	7·18	(63)	7 19	(22)	NS
	AGA CS	(82)	7·20	(56)	7·19	(20)	7·10	(6)	P<0.05
	SGA CS	(23)	7·23	(11)	7·12	(8)	7·17	(4)	P<0.025

except in the group of 23 SGA infants born by caesarean section; this group was therefore further analysed.

'Late' fetal heart rate (FHR) decelerations had been present in 14 of the 23 infants (11 antepartum and 3 intrapartum). Poor neurological outcome was restricted to this subgroup and growth retardation was in general more severe among these 14 infants (Table 4). Within this subgroup no relation between pH_{ua} and NNOS was found (Fig. 1). The occurrence of antepartum 'late' FHR decelerations seems therefore to be more important than the actual pH_{ua} values at birth, taking into account the absence of such decelerations in the vaginally delivered SGA infants.

In the SGA infants born vaginally the occurrence of meconium stained amniotic fluid (15·7%) was significantly more frequent than in the AGA group (8·6%) ($\chi^2 = 9{\cdot}0$; P<0·01). No significant relations, however, were found between the presence or absence of meconium

Table 3. Percentages of variance (R^2) in neonatal neurological optimality score (NNOS) explained by some clinical incidences of asphyxia at birth (BE, ΔBE, ΔpH and Apgar scores) according to birthweight centile and mode of delivery

	Vaginal delivery					
	Small-for-gestational age (SGA)				Caesarean section	
	Severe ($n = 46$)	Moderate ($n = 178$)	Total ($n = 224$)	AGA ($n = 805$)	SGA ($n = 23$)	AGA ($n = 82$)
Best single variable	BE	AS1	AS1	AS1	ΔBE	ΔBE
R^2	15·4	2·5*	3·8**	0·9**	84**	9
Combination	AS1+BE	AS1+ΔBE	AS1+ΔBE	AS1+ΔpH	AS3+ΔBE	AS1+ΔBE
R^2	20·3	7·0*	5·6*	1·5**	93**	22
All variables†						
R^2	22·1	7·1*	7·1*	2·0*	93**	26

* $P<0·05$; ** $P<0·025$.

† 1- and 3-min Apgar score, pH_{ua}, ΔpH, BE, ΔBE and meconium.

R2, Squared multiple correlation coefficient.

AS1 and AS3, Apgar scores at 1 and 3 min respectively.

BE, Base excess; ΔBE and ΔpH, differences between maternal and umbilical artery values

Severe SGA, <2·3 birthweight centile; moderate SGA, 2·3–10th centile; AGA, >10th centile.

Table 4. Differences in birthweight, pH variables and neurological outcome in 23 small-for-gestational age infants born by caesarean section by fetal heart rate (FHR) pattern

				Neonatal neurological diagnostic category			
FHR pattern	Birth-weight	pH_{ua}	ΔpH_{m-ua}	Normal (n)	Suspect (n)	Abnormal (n)	NNOS (median)
Late decelerations ($n = 14$)	2271 (404)	7.14 (0·09)	0.22 (0·07)	3	7	4	51·6
Normal ($n = 9$)	2601 (313)	7·25 (0·05)	0·12 (0·08)	8	1	0	56·0

NNOS, Neonatal neurological optimality score (Touwen *et al.* 1980)

Results are means (SD) where appropriate.

$P<0·01$ for measured variables.

and the Apgar scores or pH variables, nor with the neonatal neurological condition.

Discussion

Even when born at term, SGA infants, especially those with a birthweight below the 2·3 centile, show more neurological abnormalities than AGA infants. Within the frequently used definition of SGA, based on birthweight for gestation, it is not possible to differentiate between babies which are genetically small and those who are abnormally small as a result of interference with growth (congenital infection, drug exposure, reduced supply caused by chronic uteroplacental insufficiency). Severe growth retardation is probably the result of chronic uteroplacental insufficiency. Because fetal asphyxia is often the terminal event in this sequence, it is not surprising that in the subgroup below the 2·3 centile the highest association between indicators of 'asphyxia' and the neonatal neurological condition is found.

From the literature it is evident that in term SGA infants, not only short-term morbidity but also late sequelae are increased. Studies at 4–7 years of age (Fitzhardinge & Stevens 1972; Neligan *et al.* 1976) established low rates of cerebral palsy, other major neurological deficits and mental retardation but a fairly high rate of 'mini-

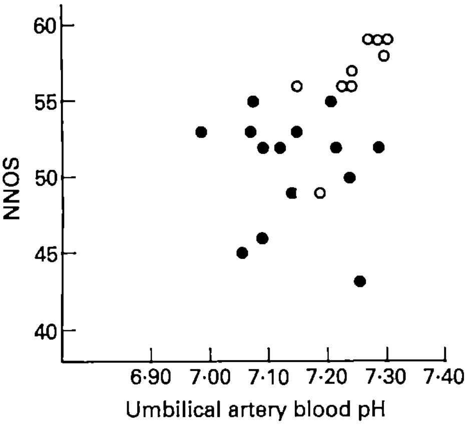

Fig. 1. Relation between umbilical artery blood pH and the neonatal neurological optimality score (NNOS) in 23 small-for-gestational age infants born by caesarean section ($r = +0{\cdot}41$; $P<0{\cdot}05$). Nine infants (○) had no fetal heart abnormality ($r = +0{\cdot}67$; $P<0{\cdot}05$); 14 infants (●) had 'late' fetal heart rate (FHR) decelerations ($r = -0{\cdot}13$; P = NS).

mal cerebral dysfunction' (speech and language problems, minor neurological findings, school failures etc). Preliminary data from the Groningen Perinatal Project show a similar tendency (Touwen 1985). The more prolonged the period of growth retardation (Harvey *et al.* 1982) and the more severe growth delay (Neligan *et al.* 1976) the less likely the growth deficit was to be completely recoverable and the more it was found to be associated with neurological abnormalities (Wallis *et al.* 1977).

In preterm SGA infants the occurrence of neurological abnormalities in the neonatal period (Huisjes *et al.* 1980) and at a later age (Drillien *et al.* 1980) has been reported to be more frequent than in term SGA infants. This may be due to the prematurity at birth, but also because the process of growth retardation in such children is likely to have begun earlier in pregnancy. In order to separate clearly those two groups in the present study only data on term SGA infants are given.

The poorer neurodevelopmental outcome in SGA infants can be explained by chronic nutritional deprivation of the brain (Gross *et al.* 1978) or by damage caused by asphyxia (Marriage & Davies 1977). Morphological findings in growth-retarded infants (Dobbing 1974) and in animal models (Bedi 1984) show a smaller brain size, fewer cells, deficits in synapse-to-neurone ratios, reduced dendritic growth etc, rather than distinct neuropathological varieties of neonatal hypoxicischaemic encephalopathy, as can be found after asphyxia (Kreusser & Volpe 1984).

The present data in SGA infants born at term indicate only a small contribution of intrapartum asphyxia, as signalled by Apgar scores and blood gas measurements to neonatal neurological morbidity. In those SGA infants born by section, a much stronger effect of prenatal fetal heart rate (FHR) abnormalities on neonatal neurology is found. 'Late' FHR decelerations are thought to indicate fetal hypoxaemia (Meyers *et al.* 1973; Bekedam & Visser 1984). From growth-retarded fetal sheep it is known that with a reduced supply line, both oxygen and glucose uptake diminish at a similar rate (Robinson *et al.* 1985). The resulting chronic hypoxaemia and hypoglycaemia were shown to be present for a prolonged period before acidaemia developed. In the present study the fetuses with 'late' FHR decelerations probably represent such a pre-existing chronic metabolic deprivation and their occurrence appears to be more important than the actual condition at birth. In the present study, a so-called 'terminal' FHR pattern, indicative of fetal acidaemia (Visser *et al.* 1980), was never found antenatally in those born by caesarean section. Acidaemia ($pH_{ua}<7{\cdot}15$) occurred only in the nine infants whose mothers were allowed to go into labour and long-lasting acidaemia was therefore unlikely to have been present.

Severely SGA infants appear more vulnerable to hypoxia than moderately growth-retarded infants: the percentage of variance in NNOS explained by the combined indicators of asphyxia was three times as high in the former than in the latter group (22% *vs* 7%). However, a squared multiple correlation coefficient of 0·22 is still low and was not statistically significant in this small subgroup of 46 infants. The effect of severe asphyxia could not be studied because only 12 of the 247 SGA term-born infants with a known pH_{ua} had a $pH_{ua}<7{\cdot}0$. Seven of these were neurologically suspect and one abnormal in the neonatal period. Ten of these infants could be neurologically examined at 6 years of age and only two showed a minor neurological dysfunction. In the severely SGA infants BE and ΔBE were better related to neonatal neurological outcome than pH and ΔpH. This is in contrast to what was found in AGA term infants (Dijxhoorn *et al.* 1985). Because in severe growth retardation a metabolic acidaemia mostly develops due to anaerobic metabolism, these acid-base indicators can best be used in SGA infants to estimate the fetal and/or neonatal condition.

Of the total group of 247 SGA infants born at term with a known pH_{ua}, six were neurologically abnormal at 4–6 years of age (Hadders-Algra 1984). These six infants all belonged to the subgroup of 26 infants who were diagnosed as abnormal during the neonatal period. Two of the six were acidaemic at birth ($pH_{ua} = 7{\cdot}06$) but they were also the most severely growth retarded.

It can be concluded that although these observations do not definitely indicate a proximate perinatal cause for neurological damage in SGA mature infants, they do reduce the likelihood that intrapartum 'asphyxia' was the primary factor operating. Prolonged nutritional deprivation resulting in severe growth retardation, especially if associated with the early signs of fetal hypoxaemia, seems to be more important with respect to neonatal neurological outcome than indicators of 'asphyxia' determined at birth. Delivery should take place before prenatal signs of hypoxaemia occur. Changes in umbilical artery and fetal aortic velocity wave forms, indicative of an increased placental vascular resistance, usually precede 'late' FHR decelerations by approximately 1–3 weeks (Hernandez *et al.* 1984). With this new technique, delivery before the occurrence of hypoxaemia may prove beneficial in selected cases.

Acknowledgments

The authors are grateful for statistical and technical advice given by Dr V. Fidler and Mrs A. Olinga respectively. The Groningen Perinatal Project was supported by the Praeventiefonds and the Prinses Beatrixfonds.

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Received 17 June 1986
Accepted 26 January 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 880–883

Effect of anaemia on fetal acid-base status

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Summary. In 79 pregnancies with erythroblastosis fetalis, fetal blood was sampled to assess the level of anaemia. Significant correlations were found between the haemoglobin concentration and umbilical artery pH, bicarbonate concentration and base excess. Compensatory mechanisms help to maintain oxygen supply in anaemia but their failure is associated with hydrops fetalis.

Anaemia reduces the capacity of blood to transfer oxygen to the tissues. In the adult, a variety of compensatory mechanisms, such as a decrease in the oxygen affinity of haemoglobin by a rise in 2,3-DPG (Bellingham 1974) or increased tissue blood flow (Pennington 1974), can maintain oxygen delivery until the anaemia is very severe when decompensation occurs. However, moderate anaemia reduces the reserve to deal with other stresses, such as exercise (Viteri & Torun 1974).

To investigate the effect of anaemic hypoxia on human fetuses, we correlated umbilical vein and artery blood gas and acid-base values with haemoglobin concentration (Hb) in blood samples obtained from 79 pregnancies with erythroblastosis fetalis.

Patients and methods

In 79 pregnancies fetal blood was sampled at 18–36 weeks gestation because of a high titre of haemolytic antibody in maternal blood. All fetal blood samples had a positive direct Coombs' test and 15 pregnancies had ultrasonographic evidence of hydrops fetalis at the time of sampling. Only blood samples obtained before the first intrauterine transfusion were included in this study because of the effect of adult Hb in the fetal circulation on oxygen transfer and fetal oxygenation (Soothill *et al.* 1987*a*). An umbilical cord vessel was punctured by cordocentesis (Nicolaides *et al.* 1986) in 41 pregnancies or fetoscopically in the other 38; these techniques and transfusion policies have been described previously (Rodeck *et al.* 1984; Nicolaides *et al.* 1987*a*). Fetal blood was aspirated to assess fetal anaemia to decide the volume of blood to be transfused (Nicolaides *et al.* 1987*b*). The 300 μl sample used for this study did not increase the fetal risk since this represents, at most, 1% of the feto-placental blood volume (Nicolaides *et al.* 1987*b*). The vessel sampled was identified by observation with ultrasound of the direction of flow of the transfused blood (or a small injection of saline when no blood transfusion was given) (Nicolaides *et al.* 1986); 56 were umbilical veins and 23 arteries.

The blood was aspirated into heparinized syringes which were sealed and kept on ice until analysed within 30 min with a Corning 178 (Halstead, England) blood gas analyser. The pH, Pco_2 and Po_2 were measured and the 'actual' bicarbonate and 'in-vitro' base excess derived and automatically displayed. Full blood counts were determined with a Coulter S-Plus counter (Coulter Electronics Ltd, Luton, England). Kleihauer testing showed that all samples contained fetal red cells only.

Fetal Hb, umbilical vein Pco_2, Po_2, bicarbonate base excess and umbilical artery Po_2 and Pco_2 change with gestational age (Soothill *et al.* 1986). Fetal Hb was expressed as the percentage of normal for gestational age. The other

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measurements were adjusted for gestation by subtracting the observed value from the normal mean for gestation. For example, gestationally adjusted Po_2 was called 'hypoxia' and a value of 10 indicates the measured Po_2 was 10 mmHg less than the mean for that gestation.

Results

In the umbilical artery blood samples from rhesus affected fetuses, significant correlations were found between Hb and pH ($r = 0{\cdot}47$, $n = 23$, $P = 0{\cdot}025$) (Fig. 1), bicarbonate ($r = 0{\cdot}55$, $n = 23$, $P = 0{\cdot}006$) (Fig. 2) and base excess ($r = 0{\cdot}60$, $n = 23$, $P = 0{\cdot}003$) (Fig. 3). The relation between Hb and pH in umbilical artery blood was significantly better described by a quadratic than linear equation and the 'best fit' line was calculated. There was no significant correlation in umbilical artery blood between Hb and Pco_2 adjusted for gestation ($r = 0{\cdot}19$, $n = 23$, NS) or Po_2, adjusted for gestation ($r = 0{\cdot}01$, $n = 23$, NS).

In the umbilical vein blood samples from rhesus affected fetuses, the Hb did not significantly correlate with any of the variables measured; pH ($r = -0{\cdot}04$, $n = 56$, NS), gestation-adjusted Pco_2 ($r = 0{\cdot}05$, $n = 56$, NS), gestation-adjusted Po_2 ($r = 0{\cdot}05$, $n = 56$, NS), gestation-adjusted bicarbonate ($r = 0{\cdot}07$, $n = 56$, NS) or gestation-adjusted base excess ($r = 0{\cdot}03$, $n = 56$, NS).

The correlations between the Hb and the umbilical artery blood acid-base measurements were not significant when the cases with fetal hydrops were excluded.

Discussion

The significant correlations between Hb and umbilical artery acid-base values indicate that severe anaemia can cause fetal tissue hypoxia. The normal umbilical vein blood values indicate that the placenta removes the acids produced by the fetus. When this mechanism fails, presumably a vicious circle of increased acidosis develops until death occurs. The difference between umbilical artery and vein blood values show that to assess the condition of the fetus, umbilical artery blood should be obtained, whereas to investigate placental function umbilical vein blood is likely to be more informative.

In a previous study plasma lactate concentration was found to rise in umbilical artery and vein blood at Hb concentrations of 8 and 4 g/dl respectively (Soothill *et al.* 1987*b*). Umbilical artery plasma lactate concentration became abnormal at less severe levels of anaemia than the other variables studied and the rise in umbilical vein plasma lactate was the only abnormality found in umbilical vein blood at any Hb. This measurement appears to be a more sensitive indicator of chronic fetal hypoxia than the traditional blood gas and acid-base values.

The adult compensates for anaemia by increasing tissue blood flow (Jacobs 1974). This is likely to occur in the rhesus affected fetus since Doppler ultrasound studies have shown increased blood velocities in anaemic fetuses (Rightmire *et al.* 1986; Kirkinen & Jouppila 1983; Gill *et al.* 1984). In sheep, fetal oxygen supply was reduced by lowering the maternal inspired oxygen percentage (Peeters *et al.* 1979). As the oxygen content fell, blood flow increased

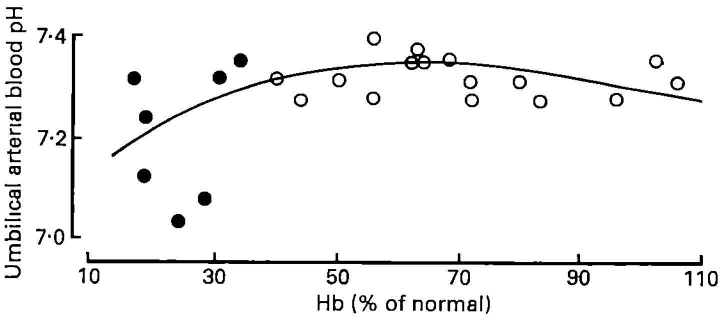

Fig. 1. Relation between haemoglobin (Hb) concentration (expressed as the percentage of normal for gestational age) and pH in umbilical artery blood ($r = 0{\cdot}47$, $n = 23$, $P = 0{\cdot}025$) The relation was significantly better described by a quadratic equation and the 'best fit' line is presented. (○) Fetuses without hydrops fetalis; (●) fetuses with hydrops fetalis

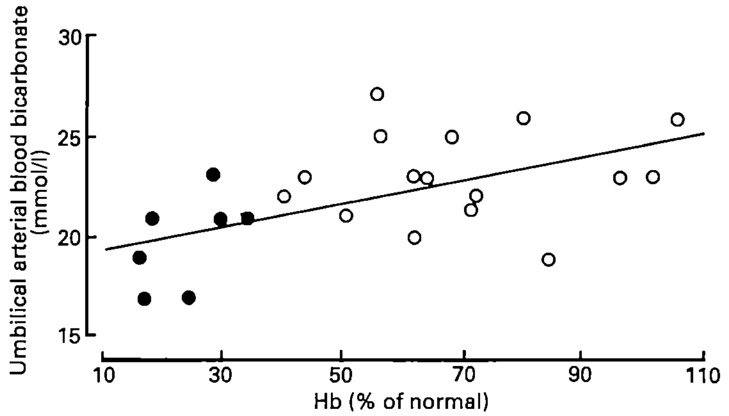

Fig. 2. Relation between haemoglobin (Hb) concentration (expressed as the percentage of normal for gestational age) and bicarbonate in umbilical artery blood ($r = 0{\cdot}55$, $n = 23$, $P = 0{\cdot}006$). (○) Fetuses without hydrops fetalis; (●) fetuses with hydrops fetalis

to all tissues until a critical level, below which there was a redistribution of blood flow in favour of the most vital organs, such as the brain and heart. This fall in blood flow to some organs produced tissue hypoxia and a decrease in the blood bicarbonate concentration. Similar results were obtained when anaemia was produced by exchanging fetal blood for plasma in sheep (Fumia *et al.* 1984). In response to severe anaemia, there was a redistribution of oxygen delivery in favour of the most vital organs. The fall in oxygen delivery to some fetal tissues was associated with umbilical artery acidosis and base deficit. Similar mechanisms in man would explain the ability of the fetus to maintain normal blood gas and acid-base measurements until the Hb fell to approximately one third of normal (4–6 g/dl depending on gestational age) when a decrease in pH and bicarbonate and increase in base deficit and lactate concentration occurs.

In the adult, the inability to sustain the increased cardiac output leads to congestive cardiac failure, fluid retention and tissue hypoxia (Jacobs 1974). A similar sequence of events may occur in the development of fetal hydrops. Supportive evidence is provided by Doppler studies of the velocity of blood in the aorta of human fetuses, which showed that the initial increase in response to anaemia was followed by a decrease

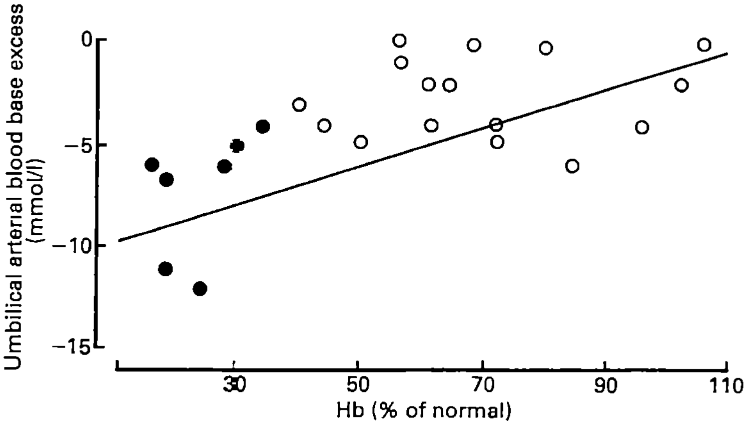

Fig. 3. Relation between haemoglobin (Hb) concentration (expressed as the percentage of normal for gestational age) and base excess in umbilical artery blood ($r = 0{\cdot}60$, $n = 23$, $P = 0{\cdot}003$). (○) Fetuses without hydrops fetalis; (●) fetuses with hydrops fetalis.

when fetal hydrops developed (Bilardo *et al.* 1987).

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Received 24 October 1986
Accepted 20 December 1986

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 884–888

The obstetric and gynaecological implications of pseudoxanthoma elasticum

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Summary. The obstetric aspects of 54 pregnancies in 20 women with pseudoxanthoma elasticum (PXE) have been reviewed. Forty live births were delivered vaginally, three of them were preterm. Twelve pregnancies miscarried at between 6 and 14 weeks gestation and two were terminated in the 8th week for psychiatric reasons. Fetal losses in two instances were attributed to cervical incompetence. One baby died at 4 days of age from a complex congenital cardiac anomaly. No abnormal maternal genital or gastrointestinal bleeding was recorded. Hypertension complicated seven pregnancies. Abdominal striae developed in all patients, the severity of which correlated with weight gain and the number of pregnancies. All the women had normal gynaecological histories, none had excessive menstrual bleeding or increased episodes of menorrhagia. The eye, blood vessels and other organ systems involved in PXE were unaffected by pregnancy. Apart from the increased risk of first trimester miscarriage and the cosmetic deterioration of the abdominal skin, there are few serious complications in pregnancy in patients with PXE.

Pseudoxanthoma elasticum (PXE) is a rare, heritable disorder of elastic fibres which is found in all population groups throughout the world. Initially described by Rigal (1881), it was at first thought to be related to the lipid disorders. The name 'pseudoxanthoma elasticum' was suggested by Darier (1896) to describe the xanthoma-like plaques found in the skin flexures. Characteristic fragmentation and calcification of elastic fibres seen histologically is pathognomonic for the disorder.

PXE is heterogeneous and four clinically distinct types have been described, two of which are inherited as an autosomal dominant trait (Pope 1974*a*) and two are inherited as autosomal recessives (Pope 1974*b*). PXE is a multisystem disorder affecting predominantly small and medium-sized arteries, Bruch's membrane in the eye and the flexural skin creases. Episodes of epistaxis and gastrointestinal haemorrhage have been reported frequently (Eddy & Farber 1962; McKusick 1973).

The potential problems for both mother and fetus during pregnancy in this disorder are many. Hypertension, intrauterine growth retardation, thromboembolic phenomena and gastrointestinal haemorrhage are some complications reported previously. Yet in a thorough literature search, only 28 pregnancies in 10 women with PXE could be identified (Berde *et al.* 1983; Lao *et al.* 1984; Elejalde *et al.* 1984). No references to gynaecological sequelae in PXE were discovered. In an attempt to elucidate these aspects further we have reviewed in detail the gynaecological histories and medical aspects of 54 pregnancies in 20 affected women.

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Patients and methods

Sixty-four patients with PXE were studied in a nationwide, multidisciplinary investigation within Southern Africa. Patients were referred by colleagues, who knew of our special interest in the disorder, to genetic clinics held in the major population centres throughout the country.

The 64 affected persons, 40 of whom were female, were derived from 34 separate kindreds. A detailed history of the disorder was obtained and all persons were examined clinically by one author (D.V.). In addition, detailed studies were performed by colleagues in the cardiac, dermatological and ophthalmic specialties. Diagnosis was confirmed by skin biopsy in every instance. Other special investigations included a radiographic survey, cineangiography of the retina, electrocardiography, echocardiography and electron microscopic examination of biopsies of affected skin.

As part of this study, gynaecological and obstetric histories were obtained and, where possible, the information was verified with hospital records. In this manner, details on the obstetric aspects of 20 women and 54 pregnancies were retrospectively obtained together with information about three placentas which had been studied macroscopically and histologically.

Results

Retrospective data were deemed sufficiently well documented in 20 women with PXE for inclusion in the investigation. Genealogical data from respective kindreds indicated that all the patients had an autosomal recessively inherited form of the disorder. Eighteen women were of white European descent and two were of mixed ancestry. At the time of the study, their ages ranged from 15 to 64 years.

Gynaecological aspects

The mean age at menarche was 13·2 years (range 11·5–15·0 years). Only five women claimed to have had menorrhagia and the average menstrual cycle was 28·2 days (range 12–32 days) with bleeding for 4·6 days (range 2–9 days). On direct questioning, eight women complained of dysmenorrhoea.

More than one third of the 20 patients were receiving oral contraceptives at the time of the study and half those questioned had previously used this form of contraception for a period exceeding 6 months. Seven women had had an intrauterine device fitted and nine women eventually opted for tubal ligation. No complications from the use of oral contraceptives were recorded.

Few of the women investigated had required operative gynaecological procedures. Three women had had a total hysterectomy; in two this was ostensibly for dysfunctional uterine bleeding in association with a fibroid uterus. In the third the procedure was advised for ovarian carcinoma with postoperative radiotherapy. She has remained well and disease free 5 years later. Surgical repair of a cystocoele and rectocoele was required in two women following the development of urinary incontinence in the fourth decade of life. In every instance the operations, anaesthesia and postoperative courses were uneventful.

Obstetric aspects

A total of 54 pregnancies were recorded in the 20 women studied. There were 40 live births and 10 first trimester spontaneous abortions. One woman with cervical incompetence had two abortions both in the second trimester. Her subsequent pregnancies were managed successfully with a Shirodkar suture. Two terminations of pregnancy were performed at 8 weeks for psychiatric reasons in one patient. Hypertension, which occurred in seven women, was treated with bed-rest alone in three and with antihypertensive and diuretic therapy in the other four. No instances of antepartum haemorrhage or diabetes mellitus were recorded in any patients. Routine antenatal ultrasound studies in seven pregnancies detected no fetal abnormalities.

A detailed history of labour was available for 38 pregnancies. Duration of the first stage of labour varied between 3 and 12 h (mean 7·3 h). All the babies were born vaginally and their mean birthweight was 3·16 kg (range 1·37–3·92 kg). Three babies were born preterm at estimated gestational ages of 32–34 weeks. No complications were associated with prematurity in these infants. Data were available for three placentas; apart from a slightly excessive degree of calcification in two and a mildly elevated placental–fetal mass ratio of 1:8 (normal 1:5–1:7), no macroscopic or histological abnormalities were detected.

Postpartum haemorrhage was not a feature of any delivery. One baby died at the age of 4 days from a complex cyanotic cardiac malformation. All the remaining live born babies, many of whom are already adults, have thrived.

There was no deterioration in the general health of the 20 women and no ophthalmological symptoms were reported during the pregnancy. Striae and the peau d'orange mottling of the skin typical of PXE became more prominent during the pregnancy, particularly in women who gained excessive weight and in some multiparas. The skin lesions did not regress after delivery and several women complained of persistence of an abdominal 'apron' of lax skin. The appearance and severity of other flexural skin lesions remained constant (Fig. 1).

Discussion

PXE is a rare heterogeneous disorder of elastic fibres which has a wide ethnic and geographical distribution. The estimated prevalence varies but is thought to be in the region of 6 in 10^6 of the population. Multiple body systems are involved due to the presence of abnormally fragmenting elastic fibres within affected tissues but the sites of predilection are the skin, cardiovascular system and eye. The cutaneous features are yellow, maculopapular areas resembling 'plucked chicken-skin' or 'cobblestones' predominantly affecting the flexural areas. The lesions are progressive and the skin in the affected regions becomes lax. The cardiovascular manifestations are early arteriosclerotic changes in medium-sized arteries with the resultant propensity for hypertension, congestive cardiac failure and stroke. In the eye, the elastin-rich lamina within the retina known as Bruch's membrane is principally affected with resultant angioid streaks, retinal haemorrhages, macular degeneration and eventual blindness.

Little has been published about pregnancy in women with PXE. In a review of the literature, Berde *et al.* (1983) documented a total of 24 pregnancies in seven women. Gastrointestinal haemorrhage was a prominent feature which was reported in 8 of 20 pregnancies in five women. Berde *et al.* (1983) also described in detail one further uneventful pregnancy in a 28-year-old woman. Lao *et al.* (1984) briefly outlined the case histories of two pregnant women with PXE, one of whom had mild hypertension, and Elejalde *et al.* (1984) described in detail one pregnancy with special emphasis on the ultrasonographic findings. Other authors have

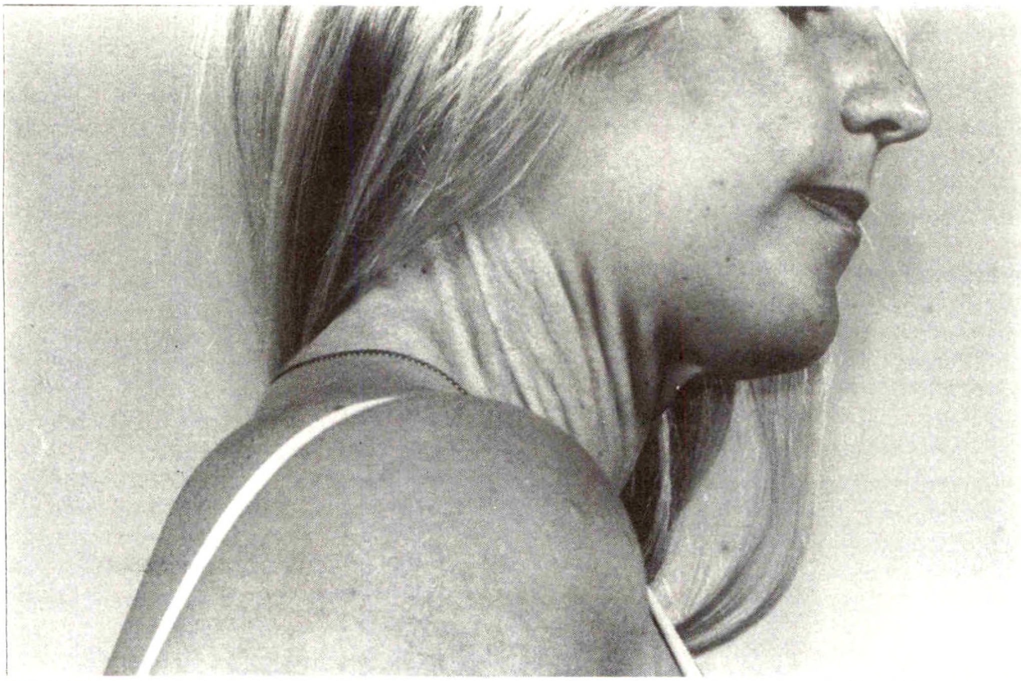

Fig. 1. Patient demonstrating the classical cutaneous laxity and peau d'orange changes of pseudoxanthoma elasticum (PXE).

alluded to obstetric complications in patients with PXE (Altman *et al.* 1981; Hall 1981) but the data presented have been insufficient for analysis. Thus far, a total of only 28 pregnancies in women with PXE have been described and these reports are probably biased in that mainly abnormal confinements would have been described.

In this paper we describe 54 pregnancies in 20 women with PXE who were part of a larger cohort of 64 affected patients, 40 of them women. The 20 women were selected for this study because detailed obstetric and gynaecological histories were available. In all these women, the medical condition was inherited as an autosomal recessive trait and the diagnosis was established by skin biopsy.

The gynaecological histories of our patients are unremarkable in that menarche occurred at the appropriate time, menstruation was normal and there was no apparent increase in episodes of menorrhagia. In view of the previously reported propensity for epistaxis, gastrointestinal haemorrhage (Carlborg 1944; Loria *et al.* 1957; McKusick 1973), ovarian haemorrhage (Giesen 1936) and uterine haemorrhage (Touraine 1940), the absence of bleeding problems in our patients suggests that these complications may have been over-reported previously in comparison to the number of normal pregnancies which take place. However, the possibility of bleeding diathesis in individuals with PXE has important implications for obstetric management.

A feature of concern in our patients was that oral contraceptives were frequently used. The risk of thromboembolic episodes is known to increase in women using high dose oestrogen oral contraceptives and in a disorder such as PXE where stroke and hypertension are more frequent, the likelihood of a vascular accident may be increased even if low dose oestrogenic compounds are used. Although we did not encounter complications of this type it would seem reasonable that other means of contraception should be advocated for these women.

Two women in our series required surgical repair of a rectocoele and cystocoele. The development of redundant folds of skin due to loss of elasticity in PXE would suggest that laxity of pelvic ligaments and tissue may also occur in multiparas, thus accounting for prolapse of bladder, rectum or uterus.

The rate of abortion in our patients (about 26%) may be slightly higher than the rate in the general population (Gustavii 1984). The two second trimester miscarriages in one woman with cervical incompetence may reflect a previously undescribed manifestation of PXE. Both miscarriages had followed a normal vaginal delivery and it could be speculated that the incompetent cervix was due to the presence of abnormal elastic fibres. However, there have been no other similar reports in the literature to support this suggestion.

Our patients had surprisingly normal pregnancies. Hypertension occurred in seven but the level and control of blood pressure improved with duration of the pregnancy suggesting that the increasing low resistance vascular bed provided by the placenta may have helped in lowering blood pressure. Despite the fact that the blood vessels are involved in PXE, no adverse cardiovascular events related to PXE were recorded during any of the pregnancies.

Labour and delivery were unremarkable in the 20 women except that there were three preterm births. This rate of premature delivery is within the normal range. Two of the three placentas examined showed mildly excessive calcification for which no reason was apparent. An important finding was that only one of the 40 babies was born with a congenital malformation; a severe cardiac anomaly which led to death at 4 days of age.

During pregnancy, no progression of the ophthalmic and cardiovascular features attributable to PXE occurred. In multiparous women, abdominal striae and marked skin laxity developed, the severity of which correlated with the number of pregnancies and excessive weight gain during pregnancy. The flexural skin lesions were unaffected during this period.

In conclusion, there was an increased risk of abortion and most women claimed a deterioration in the appearance of their abdominal skin. The potential for gastrointestinal haemorrhage due to abnormal blood vessels is present but rarely occurs in our experience. We can confirm the clinical impression that despite the potential maternal and fetal hazards, most pregnancies complicated by PXE have a normal course and outcome.

Acknowledgments

We thank Professor D. Davey for his critical comments and Diane Cannell for typing the manuscript. The investigation was supported by grants from the South African Medical Research Council, the Mauerberger Foundation, the Harry Crossley Fund and the University of Cape Town Staff Research Fund.

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Received 15 December 1986
Accepted 6 March 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 889–894

Outcome of in-vitro fertilization and embryo transfer after different regimens of ovarian stimulation

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Summary. Sixty-eight women with bilateral tubal disease and fertile male partners underwent ovarian stimulation in 187 cycles for IVF after randomization to different ovulation induction regimens. All patients initially received 150 mg clomiphene citrate on days 5–9, this regimen induced sufficient stimulation in a smaller proportion of patients than the two other regimens used subsequently which included clomiphene in combination with human menopausal gonadotrophins (hMG). The fertilization rate was significantly reduced (52·4%) in oocytes collected from cycles stimulated with hMG alone (in a small sub-group of poor responders) compared with a rate of 64·1–66·4% in cycles stimulated with clomiphene alone or in combination with hMG. Embryonic development 44–48 h after insemination was significantly retarded when clomiphene alone was utilized but a higher proportion of fragmented or abnormal embryos was observed after stimulation with hMG alone. In 118 cycles embryo transfer was performed and 20 pregnancies were established, a pregnancy rate of 16·9%. All but two pregnancies were established when two or more embryos were transferred and when the embryos were at the 4-cell or later stage of development. The regimen of clomiphene in combination with 150 i.u. hMG resulted in significantly greater numbers of oocytes recovered and embryos available per patient for transfer than the other two regimens studied.

Many studies have shown the superiority of human menopausal gonadotrophin (hMG) with or without clomiphene citrate over clomiphene citrate alone for multiple follicular recruitment and oocyte recovery (Edwards *et al.* 1980; Quigley *et al.* 1984; Vargyas *et al.* 1984; Yuen *et al.* 1985). In most of those studies more embryos were replaced in the women treated with hMG, with or without clomiphene, than in the women treated with clomiphene only, apparently a reflection of the increased number of oocytes recovered, but the subsequent pregnancy rate has been variable. Whereas Edwards *et al.* (1980) and Quigley *et al.* (1984) did not observe any significant difference in pregnancy rate with the different regimens, Vargyas *et al.* (1984) found a lower pregnancy rate with clomiphene citrate alone. It has been suggested that the anti-oestrogen effect of clomiphene (Bandendistel *et al.* 1978; van der Merwe *et al.* 1985) may have some adverse effect on the oocyte. Premature exposure of the immature oocyte to relatively high levels of luteinizing hormone (LH) may also interfere with its normal physiological function, affecting its ability to be fertilized and cleave normally (Stanger & Yovich 1985). Superovulation regimens have also been associ-

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ated with shortening of the luteal phase particularly apparent in hMG stimulated cycles (Edwards *et al.* 1980; Quigley *et al.* 1984), and this may influence the success of implantation.

The information available so far has been based on studies involving rather small numbers of cycles and therefore oocytes. Also the studies have only compared, at the most, two regimens of stimulation in identical culture systems.

We report the outcome of an in-vitro fertilization (IVF) programme following various regimens of stimulation used simultaneously over a period of 18 months, during which the protocol of clinical and laboratory procedure and staffing remained constant.

Patients and methods

Sixty-eight women with tubal disease underwent 149 laparoscopic oocyte recoveries over the 18-month study period. In all couples there were no male factors and all semen analyses fulfilled the WHO criteria for sperm density, morphology and motility. All patients were known to have accessible ovaries from previous laparoscopic assessment. Ovarian stimulation was with clomiphene citrate or hMG alone or in combination. Follicular growth was monitored ultrasonically and human chorionic gonadotrophin (hCG) was administered only when two or more follicles exceeded 17 mm mean diameter. All 68 patients initially received 150 mg clomiphene citrate daily on days 5–9 of the cycle (treatment 1), they were then randomly allocated to receive either treatment 2 (150 mg clomiphene daily on days 2–6 and 75 i.u. hMG i.m. on days 7–11) or treatment 3 (150 mg clomiphene daily on days 2–6 and 150 i.u. hMG i.m. on days 5–9).

If adequate stimulation occurred in the first treatment cycle of treatment 2 or 3, the same regimen was repeated if the patient failed to conceive. If these treatment regimens failed to induce two or more mature preovulatory follicles the patient was given 150 i.u. hMG alone daily on days 2–9 to establish whether adequate stimulation could be achieved.

Semen preparation and oocyte fertilization

The technique of semen preparation was as described by Mahadevan & Baker (1984) and used Earle's medium with penicillin and streptomycin at pH 7·35 with an osmolality of 280–290 mosmol/l. Between 50 000 and 100 000 capacitated spermatozoa were used for insemination of each oocyte in a 0·1 ml drop of medium under sterile non-toxic liquid paraffin. Oocytes were incubated at 37 °C in a humidified atmosphere of 5% O_2, 5% CO_2 and 90% N_2. Fertilization was confirmed by the presence of two pronuclei 16–20 h after oocyte insemination and subsequent embryonic cleavage.

Embryos were assessed for normal development 44–48 h after insemination and were considered unsuitable for transfer if cleavage after fertilization was abnormal from morphological criteria of evenness of blastomeres, intact zona and intact cells (Pike 1984).

Embryo transfer

Embryos were transferred 44–48 h after insemination using the Wallace embryo transfer catheter (H. G. Wallace Ltd, UK) with the patient in the lithotomy position. Embryos were replaced in 10–15 μl of medium containing 50% maternal serum, and patients were kept in bed for 18–24 h before being discharged home. No luteal phase support was administered. All pregnancies were confirmed by a rising titre of serum β-hCG from 12 days after embryo transfer and ultrasound demonstration of the gestation sac 4 weeks after the transfer. 'Biochemical pregnancies' alone have not been included.

Statistical analysis

Statistical analysis was by Student's *t*-test and test of significance of differences between proportions (percentage).

Results

Response to stimulation regimens

At the onset of the study patients were randomly allocated to receive either treatment 2 or treatment 3 after the initial course on treatment 1 (clomiphene citrate alone) which all subjects received. At least two spontaneous menstrual cycles occurred between each treatment cycle. The patients were thus divided into two main comparative groups: group A had received treatments 1 and 2 and group B had received treatments 1 and 3. There was no difference in the mean ages between the two groups: 29·1 (SD

3·4) and 28·4 (4·2) years in groups A and B respectively.

The results of the response to stimulation treatments, the number of oocytes recovered and the outcome of oocyte insemination are shown in Table 1.

The two groups A and B responded similarly to the initial treatment 1 with clomiphene alone with about 70% of cycles showing sufficient stimulation to allow oocyte recovery. The other two treatment regimens (2 and 3) were superior to treatment 1 (clomiphene alone) in the percentage of patients who responded adequately in their first treatment cycle. Treatment 3 was better than treatment 2 with 88·2% of patients having sufficient stimulation in the first cycle. No patient experienced the clinical hyperstimulation syndrome.

Although the number of oocytes recovered per patient increased with the different treatment regimens, the overall percentage of oocytes which fertilized did not differ between the various stimulation regimens. This indicates that the proportion of immature oocytes recovered with treatments 2 and 3 was no higher than that with treatment 1, and this was confirmed by morphological maturity assessment of the recovered oocytes.

The percentage of patients having oocyte recovery who subsequently underwent embryo transfer did not differ between treatments 1 and 2 (70·6% and 69·0% respectively) but was significantly greater at 92·1% on treatment 3 ($P<0{\cdot}002$). The number of normal embryos available for transfer was also significantly greater with treatment 3 than with treatment 1 ($P<0{\cdot}001$).

Six patients (four from group A, two from group B) who had failed to respond to either of their two previous treatment regimens were then stimulated with hMG alone (treatment 4), after which 83·3% of 12 treatment cycles achieved adequate stimulation but only 52·4% of the oocytes recovered could be fertilized.

Embryonic development

The developmental stages of all the fertilized oocytes 44–48 h after insemination are shown in Table 2. Most embryos (56·5%) were at the 3–4 cell stage. A significantly higher proportion (20·0%) of the embryos from the cycles stimulated with clomiphene only (treatment 1) were under 4 cells compared with 5·4 and 11·5% from cycles stimulated with treatments 2 and 3, respectively ($P<0{\cdot}05$). Although there was no significant difference in the proportion of morphologically abnormal embryos between the treatment regimens, an unusually high proportion (27·3%) of embryos from the cycles stimulated with hMG only was recorded as abnormal or fragmentary.

Twenty clinical pregnancies were achieved after embryo transfer in 118 cycles, a pregnancy rate of 16·9%. All but two of the pregnancies were attained after the replacement of two or

Table 1. Outcome of various ovulation induction regimens used for an in-vitro fertilization programme

	Group A		Group B	
	Treatment 1 (150 mg cc)	Treatment 2 (150 mg cc+hMG 75)	Treatment 1 (150 mg cc)	Treatment 3 (150 mg cc+hMG 150)
Number of patients	34	30	34	34
Adequate stimulation in first treatment cycle	24 (70·5%)	24 (80%)	23 (67·6%)	30 (88·2%)
Total number of cycles	34	37	34	70
Cycles with oocyte recovery	24	29	23	63
% patients with oocyte recovery	70·6%	69·0%	67·6%	92·1%
Number oocytes recovered	53	85	47	235
% fertilized	64·1%	65·9%	65·7%	66·4%
Number cycles having embryo transfer	17	20	17	53
Number of embryos/patient mean (SD)	1·5 (0·7)	2·2 (0·9)	1·4 (0·9)	2·5 (1·4)
Number pregnant	4	2	0	12

cc, Clomiphene citrate; hMG, human menopausal gonadotrophin.

Table 2. Stage of development of embryos 44–48 h after insemination. Differences between ovulation induction regimens

Embryonic stage (no. of cells)	Treatment 1 (150 mg cc)	Treatment 2 (150 mg cc + 75 i.u. hMG)	Treatment 3 (150 mg cc + 150 i.u. hMG)	Treatment 4 (150 i.u. hMG)
2	13 (20·0%)	3 (5·4%)	18 (11·5%)	3 (13·6%)
3–4	35 (53·8%)	35 (62·5%)	90 (57·7%)	9 (40·9%)
5–7	4 (6·2%)	8 (14·3%)	19 (12·2%)	3 (13·6%)
>8	4 (6·2%)	4 (7·1%)	12 (7·7%)	1 (4·6%)
Abnormal/fragmentary	9 (13·8%)	6 (10·7%)	17 (10·9%)	6 (27·3%)
Total	65	56	156	22

cc, Clomiphene citrate; hMG, human menopausal gonadotrophin.

more embryos. Similarly, all but two pregnancies occurred when at least one 4-cell embryo was replaced. The two pregnancies achieved when only 2-cell embryos were replaced terminated in miscarriages at 7 and 8 weeks. The outcome of the pregnancies is shown in Table 3. One cornual ectopic and five miscarriages occurred.

Two twin pregnancies have been delivered and two other pregnancies showed twin gestation sacs with fetal hearts, in which one sac collapsed subsequently at 7 and 9 weeks with

Table 3. Number and development stage of embryos at transfer and pregnancy outcome

Stimulation regimen	Developmental stage of embryos (no of cells) 2	3–4	5–6	>8	Total	Pregnancy outcome (weeks gestation)
Treatment 1						
(150 mg clomiphene)	—	2	—	—	2	Live male (37)
	—	2	—	—	2	Live male (38)
	2	—	—	—	2	Miscarriage (8)
	—	—	2	1	3	Live female (40)
Treatment 2						
(clomiphene + 75 i.u. hMG)	—	2	1	—	3	Ruptured cornual ectopic (10)
	—	1	—	—	1	Live male (39)
Treatment 3						
(clomiphene + 150 i.u. hMG)	—	2	—	—	2	Live female (36)
	3	—	—	—	3	Miscarriage (7)
	—	3	—	—	3	Live female (37)
	—	3	—	—	3	Live female (34)
	—	—	1	—	1	Miscarriage (7)
	—	2	2	—	4	Live dizygotic female twins (37)
	—	1	1	—	2	Live male (40)
	—	5	2	—	7	Live dizygotic male twins (38)
	—	—	2	3	5	Missed abortion (11)
	—	3	1	1	5	Twin pregnancy, one live male (37)
	—	2	1	1	4	Live female (38)
	2	3	1	—	6	Twin pregnancy, one live female (39)
Treatment 4						
(150 i.u. hMG)	—	1	1	—	2	Miscarriage (7)
	1	3	—	—	4	Live male (40)

singleton pregnancies proceeding. All the twin pregnancies occurred when four or more embryos were transferred and this has led to a policy of no more than four embryos now being replaced. Sixteen babies have been born, none with any congenital anormality.

Discussion

Multiple embryo transfer has been an important contribution to the improved pregnancy rate associated with IVF and embryo transfer (Edwards & Steptoe 1983). This has encouraged the use of various ovarian stimulation regimens to achieve multiple follicular development, although it is known that the conventionally used drugs, clomiphene citrate and hMG, may have adverse effects on the genital tract tissue (Bandendistel *et al.* 1978; van der Merwe *et al.* 1985) or the oocytes themselves (Jeffcoate 1985). Garcia *et al.* (1983) reported a possible acceleration of endometrial development in cycles stimulated with hMG only, but the effect of this is not known.

Our findings suggest that apart from the poorer outcome, in terms of follicular recruitment, from cycles stimulated with clomiphene only, the fertilization rate is little less than that observed with hMG with or without clomiphene. Embryonic development, however, appears retarded in oocytes obtained from cycles stimulated with clomiphene alone as is shown by the higher proportion of 2-cell embryos at 44–48 h. This retardation may be explained by the late administration of clomiphene on days 5–9 of the cycle and hence a possible residual anti-oestrogenic effect on the follicular environment and oocyte. This is supported by the fact that with the other two induction treatments where clomiphene was discontinued earlier, embryonic development was comparable. The relatively high proportion of abnormal embryos associated with the hMG-only regimen is worrying and might suggest that a large proportion of the oocytes recovered are physiologically abnormal. The rather early exposure of oocytes to relatively high levels of LH from day 2 of cycle may be a possible explanation (Jeffcoate 1985).

The replacement of one or more embryos at the 4-cell stage or later is associated with an increased likelihood of pregnancy. Conversely, an embryo only at the 2-cell stage at 44 h after insemination, whilst appearing morphologically normal, seems to have a reduced chance of establishing a pregnancy. Larger numbers need to be analysed but it seems not unlikely that the delay in embryonic development may indicate some inherent abnormality and lack of potential for continued growth and lead to further loss of vital synchrony with the endometrium.

These data from a randomized study of different ovulation induction regimens confirm earlier published data from McBain & Trounson (1984) and suggest that a combination of clomiphene and hMG (150 i.u.) provides a reliable and safe method for ovarian hyperstimulation in IVF cycles.

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Received February 1986
Resubmitted 8 January 1987
Accepted 5 March 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 895–900

Negative cone biopsies after colposcopy and their prediction

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Summary. A retrospective study of 899 cone biopsies revealed significantly more cones containing no dysplastic epithelium in patients who had a prior colposcopic assessment compared with those who had not been so assessed. A case-control study of 48 'negative' cones, 47 cones containing intraepithelial neoplasia (CIN), 44 microcarcinoma containing cones and 27 occult Ib containing cones has allowed five variables to be identified which can predict the presence of dysplastic or neoplastic tissue in the cone specimen. These variables include a colposcopic suspicion of invasion; a positive or worse pre-cone smear; two severely dyskaryotic smears within a 12-month observation period, previous abnormal histology and previous treatment for CIN. Using these criteria, 44% of 'negative' cones could be avoided without overlooking any cases of microcarcinoma or occult carcinoma.

Conization of the uterine cervix is an important diagnostic and therapeutic technique in the management of cervical intraepithelial neoplasia (CIN). Since the introduction of colposcopy and directed biopsy it has been possible to select cases for treatment by local destruction.

The adequacy of colposcopic assessment depends on seeing the whole transformation zone. If this is not possible then conization has been the recommended procedure to provide a histological diagnosis. A proportion of cone specimens do not, however, contain evidence of malign epithelium and such procedures should be regarded as sub-optimal since a diagnosis is not achieved and patients are subjected to the well-documented morbidity.

The objectives of this study were to investigate the occurrence of 'negative' cone biopsies in our patient population and to assess the impact, if any, of prior colposcopic assessment. To identify and assess which factors might be useful in selecting patients with inadequate colposcopy for conization, a case-control study of negative cones compared with cones containing CIN, early stromal invasion and occult stage I carcinoma was performed.

Materials and methods

Definition of 'negative cones'

Cones were defined as containing no evidence of malign epithelium if, on serial sectioning (minimum of 10 blocks), no evidence of dysplastic squamous or glandular epithelium was found.

Calculation of incidence

The retrospective data from our previous study (Luesley *et al.* 1985) was used in the calculation of incidence. Records from 915 patients were available of which 899 were considered suitable for accurate histopathological assessment. In 685, colposcopic assessment had been performed before the cone biopsy; 214 had had

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cone biopsy without prior colposcopic assessment. These two management policies were the result of the individual preferences of clinicians at the time and did not reflect any difference in the 'severity' of the lesion at presentation.

Case-control study

Negative cone biopsy group. Between June 1983 and December 1984, 48 patients conforming to the above definition were identified. All cone specimens were examined by the same histopathologist and all patients had two post-cone cytological and colposcopic assessments all of which were negative for a suspicion of residual CIN. The benign pathology seen within this group was: mild atypia (1); inflammatory changes only (13); koilocytosis only (2); immature metaplasia (19) and reserve cell hyperplasia (5). No specific comment was made in a further eight specimens. The median age of the women in this group was 39 years (range 23–63 years).

CIN group. Over the same observation period, June 1983 to December 1984, 47 patients with CIN were selected for the study (CIN III, 41; CIN II, 6). Cases were selected by age and parity matching with cases in the negative cone group. The median age was 39 years (range 23–57 years).

Invasive cervical cancer group. As far fewer of these patients are normally identified, an extended observation period was used (1980–1985 inclusive). The same pathologist examined all the cone specimens. Two sub-groups were identified within the invasive cancer group. There were 44 specimens with micro-invasive cancer, as defined by the RCOG International Study Group (Jordan *et al.* 1982), of which 29 showed early stromal invasion and 15 measurable lesions. Twenty-seven cases were classifiable as occult stage Ib carcinoma in that they were clinically unrecognized but demonstrated stromal invasion of >5 mm on histopathological evaluation.

Investigations before cone biopsy

All patients had at least one smear and one colposcopic assessment before conization. Twenty patients had been previously treated for histologically confirmed CIN and 67 patients had a prior histological assessment (64 directed punch biopsies; 3 cone biopsies).

Assessment of cone specimens

All specimens were examined by one pathologist (T.W.E.). The maximum width and antero-posterior dimensions of the epithelium covered base of the cone and its total length measured to the nearest millimetre after fixation in formal saline were recorded. A minimum of 10 blocks per specimen were examined.

Statistical analyses

Where indicated χ^2 analysis with Yates' correction has been used. In addition, sensitivities and specificities have been calculated for the various diagnostic procedures. Predictive values have not been computed as the case-control study does not reflect true prevalence of disease in the colposcoped population and in this disease sensitivity is the more important parameter with respect to management outcome.

Results

The prevalence of negative cone biopsies

Of the 899 cone biopsies, 152 (17%) had no evidence of dysplastic epithelium on serial sectioning. In 685 instances, prior colposcopy had been performed, in 128 of these (19%) no dysplasia was found. In 214, no prior colposcopy had been performed; 24 of these specimens (11%) contained no evidence of dysplasia. There was a significantly higher prevalence of 'negative cones' in the group colposcoped before conization ($0{\cdot}02>P>0{\cdot}01$) (Table 1).

Sensitivity of pre-conization diagnostic procedures

The case-control study included 166 patients.

Colposcopic assessment. CIN was suspected in 110 patients; microcarcinoma or worse in 34 and no lesion was seen in the other 22. The whole transformation zone was seen in 21 of the 166 colposcopies. There were four cases where the whole transformation zone was seen and considered to be normal; all had negative cones. Only 33% of all the cases of microcarcinoma or worse would have been detected if selection for

Table 1. Association of pre-conization colposcopy with the prevalence of negative cone biopsies

	Cone biopsy histology					
	CIN I	CIN II	CIN III	ESI(+)	NED	Total
Colposcoped	56	75	394	32	128	685
Not colposcoped	19	32	125	14	24	214
Total	75	107	519	46	152	899

CIN, Cervical intraepithelial neoplasia; ESI, early stromal invasion; NED, no evidence of disease.

Table 2. The selective value of colposcopic assessment of the severity of the lesion

		Cone histology		
Colposcopic assessment		Negative	CIN	ESI/invasion
No lesion	(n=22)	17	4	1
CIN	(n=110)	28	37	45
ESI/invasion	(n=34)	3	6	25
Total	(n=166)	48	47	71

Table 3. Selective value of a prior histology specimen

		Cone histology			
Prior histology		Negative	CIN	ESI	Invasion
Malign	(n=54)	13	10	18	13
Normal	(n=13)	9	2	—	2
None	(n=99)	26	35	26	12
Total	(n=166)	48	47	44	27

conization were solely based on a colposcopic suspicion of these disease states (Table 2). Thirty-one of the 48 'negative' cone biopsies had an abnormal colposcopic assessment.

Prior treatment for CIN. Twenty patients had been previously treated (CO_2 laser, 13; electrodiathermy, 1; cryocautery, 3; cone biopsy, 3). In eight cases no dysplasia was found in the subsequent cone biopsy (6 laser; 2 cone), in four CIN was found (2 laser; 1 cryocautery; 1 cone). In three cases microcarcinoma was found (2 laser; 1 cryocautery) and in five cases occult Ib carcinoma (3 laser; 1 diathermy; 1 cryocautery). Of the patients who had had previous treatment for CIN, 60% had evidence of CIN or invasion in the subsequent cone.

Previous histology. Details of prior histology are presented in Table 3. Any previous malign histology gives a sensitivity for the detection of malign epithelium in the cone of 75% and 45% of invasive disease would be detected if conization was selected only on histological grounds. If a normal pre-cone biopsy is obtained only 2% of subsequent cones will contain invasive cancer.

Pre-conization smear. Three types of smear have been categorized: positive or worse; suspicious (includes moderate and severe dyskaryosis) and negative (includes minor abnormalities). The distribution of these smear types in relation to findings in the cone biopsy is detailed in Table 4. Of the 71 patients with microcarcinoma or occult carcinoma, 61 had positive or worse cytology giving a sensitivity for the detection of invasion of 85%. Twenty-seven of the 48 negative cones had negative or minor cytological abnormalities, the sensitivity of this type of smear being only

Table 4. Selective value of the pre-conization smear

Pre-cone smear		Cone histology Negative	CIN	ESI	Invasion
Negative to mild dyskaryosis	(n=33)	27	4	1	1
Moderate to severe dyskaryosis	(n=37)	13	16	6	2
Positive to ? invasion	(n=96)	8	27	37	24
Total	(n=166)	48	47	44	27

Table 5. Selective value of cytological history

Cytological history		Cone histology Negative	CIN	ESI	Invasion
Adverse*	(n=95)	18	30	33	14
Non-adverse	(n=38)	23	5	6	4
One smear only	(n=33)	7	12	5	9
Total	(n=166)	48	47	44	27

*Two consecutive smears, positive or worse within a 12-month observation period.

Table 6. Sensitivity and specificity of individual diagnostic criteria and the effect of sequential application

Diagnostic criteria	Sensitivity for Invasion (%)	All cases (%)	Specificity (%)
1. Colposcopic suspicion of invasion	35	26	94
2. Pre-cone smear	85	75	83
3. Smear history	66	81	56
4. Prior treatment	40	60	40
5. Prior histology	45	75	41
Combined tests (1,2,3)	100	95	44

18%. Only 2% of invasive cases would be expected to have such minor cytological abnormalities.

Preceding cytological history. Differences in the interdependent variables of number of cytological assessments and duration of cytological review were recognized between the cone groups. By incorporating the severity of the cytological report and the duration of abnormality, two types of cytological history can be defined. An 'adverse' history consists of two consecutive moderately dyskaryotic smears, or worse, within a 12-month observation period. Excluding the 33 patients coned after only one smear report, 95 patients had 'adverse' cytological histories and 38 had less than 'adverse' histories. The relation between cytological history and cone histology is shown in Table 5. The sensitivity of an adverse history is 81% with a sensitivity for detecting invasive lesions of 66%. These figures fall to 39% and 14% respectively if patients were to be coned on the basis of a less than 'adverse' cytological history.

Sequential analysis of predictive variables

No single variable has a satisfactory sensitivity for the detection of microcarcinoma or occult invasive disease. The variables have therefore been combined in a sequential fashion providing five levels of selection. These data are summarized in Table 6. A 100% sensitivity for detecting microcarcinoma and occult carcinoma is achieved after three selections, i.e. patients having colposcopic stigmata of invasion will be coned; of the remainder, those with a positive smear will be coned and of those still remaining, those with an 'adverse' cytological history will be coned. Six cases (12%) of CIN would remain unselected (4 CIN II; 2 CIN III), and 21 (44%) of the negative cones would also have remained unselected.

Discussion

The use of colposcopy and directed biopsy allows a proportion of patients with CIN to be treated by local ablation. The criteria that must be met before such treatments have been well described (Jordan 1985). A dilemma arises when these criteria cannot be met, the inability to observe the whole transformation zone being the most common case in point. In such a situation, a reliable histological sample of the most atypical part of the transformation zone cannot be collected, rendering local destruction inappropriate. Faced with this situation, the colposcopist will generally elect to take a cone biopsy, thus achieving tissue diagnosis and (in the majority of instances) total removal of the lesion.

Both ourselves (Luesley *et al.* 1985) and others (Holyock & Chanen 1972) have reported that the most frequent indication to cone is the inability to observe the whole transformation zone. Our data suggest that in certain predefined situations this may not be necessary.

Conservative management, in the form of continued observation, has received little attention, partly because it is contrary to the colposcopic ethos of arriving at a histological diagnosis and also because of the ever present fear of overlooking an occult neoplastic lesion (Bjerre & Johansson 1983), the latter being particularly pertinent with regard to adenocarcinomas (Benoit *et al* 1984). We feel that these points might explain the difference in the frequency of negative cone biopsy between colposcoped and non-colposcoped patients.

Before the reintroduction of colposcopy, the decision to perform conization rested heavily on the presenting cytological characteristics, a positive smear being the most common reason for proceeding (McLaren 1967). As yet there is no evidence to suggest that colposcopy has affected the frequency of occult cancer in cone specimens, its major impact being that it allows conization to be avoided in certain circumstances. Conservative cytologically based management might therefore still have an important role.

The high specificity of a colposcopic appearance suggestive of invasion for detecting malign epithelium (although not necessarily invasion) justifies its inclusion as an indication to cone, and despite its poor sensitivity, it would be unrealistic not to expect the colposcopist to proceed in such situations. Our findings suggest that colposcopy may overdiagnose such lesions which again is in keeping with the margin of safety within which the colposcopist justifiably operates.

A positive or worse smear, or two consecutive severely dyskaryotic smears within 12 months, are also sensitive indicators suggesting that these are useful criteria on which to base management. Colposcopy or cytology alone, however, cannot confidently predict all those cases with invasive disease but in combination they are highly satisfactory.

A history of malign histology also justifies a decision to perform a cone biopsy. This is based not only on an overall sensitivity of 75% but also on data reported by McIndoe *et al.* (1984) which suggested that such patients with subsequent abnormal cytology were at a greatly increased risk of developing invasive cancer. It was noted that 13 of our 48 'negative' cones had a previous biopsy which was suggestive of malign epithelium. This observation might be explained by the lesion having been totally removed by the biopsy or by an effect on the biology of the disease by the process of biopsying (Richart & Barron 1969). The inclusion of prior treatment of CIN as an indication to cone is based on the fact that most of these patients will have had abnormal histology. One also has to consider the theoretical effect of sequestering abnormal epithelium beneath the new epithelial surface. The reported frequencies of invasive carcinoma after local ablation have been few and sporadic (Sevin *et al.* 1979; Townsend *et al.* 1981). We feel they are sufficient to justify conization where cytology is abnormal after local destructive techniques.

Implementation of our sequential selection criteria would leave no cases of invasive disease unselected. Six patients with CIN would not have been selected, two of whom had CIN III One might confidently predict that by continued cytological and colposcopic surveillance, the same criteria would subsequently select these patients.

Several authors have described the advantages of endocervical curettage in situations where colposcopy is unsatisfactory (Hatch *et al.* 1985; Drescher *et al.* 1983) and Urcuyo *et al.* (1977) suggested the addition of endocervical curettage to prevent underdiagnosis in situations where colposcopy is unsatisfactory. Talebian *et al.* (1977), however, concluded that endocervical curettage was unnecessary in patients with unsatisfactory examinations as they all required conization. Experience with endocervical curettage is limited in the UK and although we could concede that it may be beneficial in certain situations, such as an addition to our conservative regimen, it provides little advantage when a decision to perform cone biopsy has already been made.

Our data suggest that correctly applied conservative management would reduce the negative cone biopsy rate by almost 50%, equivalent to that seen prior to the introduction of colposcopy. This might be achieved without the risk of overlooking occult carcinoma.

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Received 26 September 1986
Accepted 3 March 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 901–906

Natural killer cells in cervical intraepithelial neoplasia and human papillomavirus infection

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Summary. A semiquantitative immunocytochemical study of natural killer (NK) cells in cervical mucosa was performed by the immunoperoxidase technique using anti-Leu-7 and anti-Leu-11 monoclonal antibodies. NK cells were present in two of the five normal controls and five of six specimens showing human papillomavirus (HPV) infection. Of the 12 CIN studied, six were positive for both Leu-7 and Leu-11 staining and three were positive for Leu-11 alone. NK cells were found predominantly in the subepithelial stroma. The frequency and pattern of distribution of these cells were similar in all grades of CIN. The number of NK cells present was usually small but the degree of infiltration by Leu-11 positive cells was pronounced in two HPV infections and in one CIN 1. NK cells may have a role in surveillance against HPV infection and the development and progression of CIN.

Natural immunity mediated through natural killer (NK) cells is thought to be a complementary system to adaptive cell-mediated immune surveillance in man (Moore 1985). Unlike T-lymphocytes which require specific antigen priming and sensitization by accessory cells to become activated, NK cells have a spontaneous cytotoxic effect against virally infected cells and neoplastic cells (Herberman & Ortaldo 1981; Herberman & Oldham 1983). Tumour cells devoid of major histocompatibility (MHC) antigens elude the normal adaptive cell-mediated immune reaction but are susceptible to NK cell lysis. A role for NK cells in tumour immune surveillance is supported by the findings that patients with congenital deficiency of NK activity have an increased risk of developing malignancy (Hersey *et al.* 1979; Roder *et al.* 1980). Hersey *et al.* (1982*a*) also reported a young girl with Fanconi's anaemia who had selective deficiency of NK activity but normal T- and B-cell functions and who later developed extensive genital warts, vulvar squamous cell carcinoma and carcinoma *in situ* of the cervix. Animal studies (Hanna & Fidler 1983) and human studies (Herberman & Oldham 1983; Forbes *et al.* 1980; Hersey *et al.* 1982*b*) indicate that NK cells play an important role in natural resistance against tumour *in vivo.*

We have recently demonstrated that in human papillomavirus (HPV) infection and cervical intraepithelial neoplasia (CIN) the cell-mediated immune reaction appears to be deficient as shown by depletion of Langerhans' cells (Tay *et al.* 1987*a*) and T-cells (Tay *et al.* 1987*b*). It is important to determine whether there is a NK cell response in these conditions.

Lanier *et al.* (1983) showed that all the lymphocytes expressing NK activity in the peripheral blood reacted with anti-Leu-7 (HNK-1) (Abo & Balch 1981) and anti-Leu-11 (NK-15) (Phillips & Babcock 1983) monoclonal antibodies. These antibodies have been widely used for in-situ identification of NK cells on frozen

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sections (Si & Whiteside 1983; Ritchie *et al.* 1983; Fiocchi *et al.* 1985; Gibson & Jewell 1986). We report here a semiquantitative in-situ study of NK cells using these monoclonal antibodies in biopsies from patients with HPV infection and CIN.

Subjects and methods

Patients newly referred to the colposcopy clinic for assessment of HPV infection ($n = 4$), mild dyskaryosis ($n = 8$), and moderate/severe dyskaryosis ($n = 6$) were studied. The mean ages in the three groups were 28·2, 29·5 and 25·6 years respectively. Five normal controls, mean age 32·8 years, were selected from patients who had had more than one normal cervical smear and who were undergoing elective laparoscopic sterilization.

Table 1. Degree of infiltration by Leu-7 and Leu-11 positive cells

		Degree of infiltration*	
Subject no.	Histology	Leu-7 positive	Leu-11 positive
1	Normal	0	0
2	Normal	0	0
3	Normal	0	0
4	Normal	+	0
5	Normal	+	+
6	HPVI	0	0
7	HPVI	+	+++
8	HPVI	+	+
9	HPVI	++	+
10	HPVI	+	+
11	HPVI	+	+++
12	CIN1	0	+
13	CIN1	+	+++
14	CIN1	0	0
15	CIN1	0	0
16	CIN1	+	+
17	CIN1	+	++
18	CIN2	0	0
19	CIN3	+	+
20	CIN3	0	+
21	CIN3	0	+
22	CIN3	+	++
23	CIN3	+	+

* 0 = none; + = <10 cells; ++ = 10–20 cells; +++ = >20 cells.

Biopsies

Two colposcopically directed adjacent punch biopsies from the same lesion in the transformation zone were obtained from the patients. Two similar punch biopsies were taken near the external os from the controls under general anaesthesia at the time of laparoscopy. In each case, one biopsy was snap frozen in liquid nitrogen and the other fixed in formol sublimate for routine histology.

Immunocytochemical staining

Fresh frozen sections at 10 µm thickness were cut, dried at room temperature, fixed in acetone for 10 min and rehydrated with Tris-HCl buffered saline (TBS), pH 7·4. An indirect immunoperoxidase method using anti-Leu-7 and anti-Leu-11 antisera at 1 in 4 dilution, and peroxidase conjugated rabbit anti-mouse anti-sera (Dako P260) at 1 in 200 dilution was performed as described previously (Tay *et al.* 1987*b*). Freshly prepared 3,3′-diaminobenzidine (0·5 mg/5 ml) with 0·05% hydrogen peroxide was used as the chromogen. The sections were counter-stained with haematoxylin.

Grading of NK cell infiltration

The sections were examined under a light microscope (Leitz Wetzlar) at 400 times overall magnification. NK cells were identifiable as mononuclear cells with positive membranous staining. The degree of NK cell infiltration was expressed semiquantitatively at four grades according to the number of positive cells seen in each high power field: 0 (none); + (<10 cells); ++ (10–20 cells); +++ (>20 cells).

Results

The final diagnosis, based on the criteria of Buckley *et al.* (1982) and Dyson *et al.* (1984), showed that there were six simple HPV infection, six CIN 1, one CIN 2 and five CIN 3. All patients with CIN showed histological evidence of HPV infection. None of the controls showed any abnormalities.

The results of anti-Leu-7 and anti-Leu-11 staining are summarized in Table 1.

In the normal cervix, Leu-7 positive cells were present in small numbers (+) in only two of the five biopsies. Only one specimen showed posi-

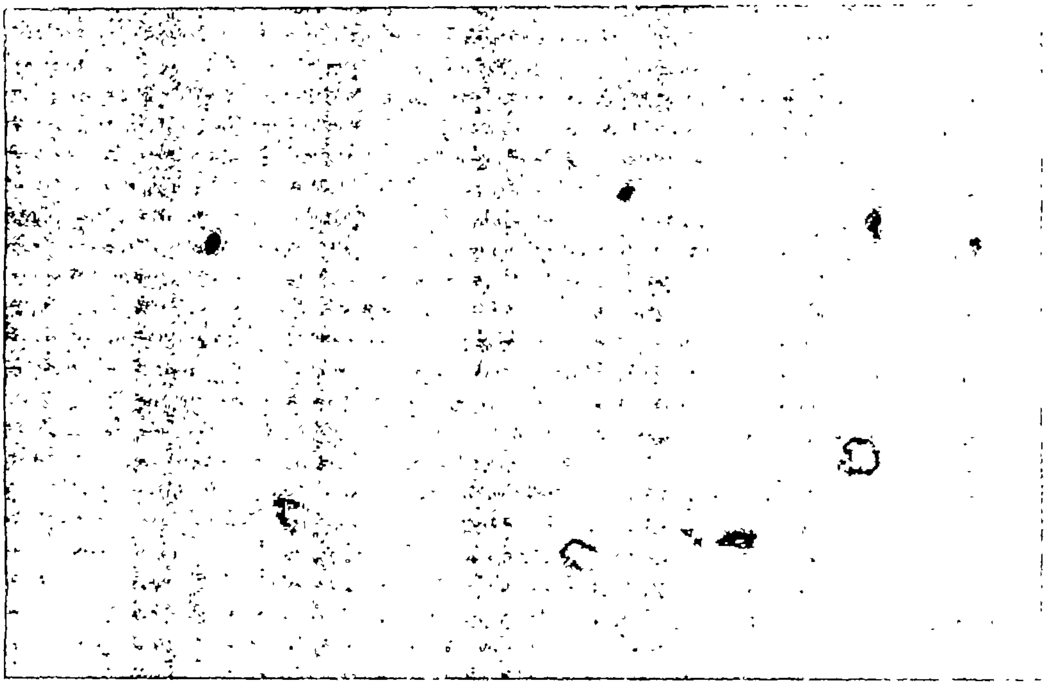

Fig. 1. Photomicrograph showing a small number of Leu-7 positive NK cells in the stroma from a patient with simple HPV infection of the cervix. ×400.

tive staining for anti-Leu-11; this was one of the two Leu-7 positive specimens and Leu-7 and Leu-11 positive cells were present only in the subepithelial stroma but not in the epithelium.

The Leu-7 positive and Leu-11 positive cells were present simultaneously in five of the six biopsies showing HPV infection without neoplasia. The number of Leu-7 positive cells was small (+) in four and moderate (++) in one (Fig. 1). Two of the five specimens showed pronounced infiltration (+++) by Leu-11 positive cells (Fig. 2). Both Leu-7 and Leu-11 positive cells were seen predominantly in the stroma. One of the six was negative for both Leu-7 and Leu-11.

The pattern of distribution and degree of infiltration by Leu-7 and Leu-11 positive cells were similar for all grades of CIN. Both Leu-7 and Leu-11 positive cells were simultaneously found in the stroma in six of the 12 biopsies and Leu-11 positive cells alone were found in another three. The number of Leu-7 positive cells was small (+) but the infiltration by Leu-11 positive cells was moderate (++) in two (Fig. 3) and pronounced (+++) in one. Three of the 12 cases did not show any Leu-7 or Leu-11 positive NK cells.

Discussion

In the present study NK cells were identified by the well-established markers, Leu-7 (HNK-1) and Leu-11 (NK-15) antigens, and cells other than mononuclear cells were excluded on strict morphological criteria. Using these two markers in a two-colour immunofluorescence flow cytometric study, Lanier *et al.* (1983) classified peripheral lymphocytes into four subsets: Leu-7+/Leu-11−, Leu-7+/Leu-11+, Leu-7−/Leu-11+ and Leu-7−/Leu-11− cells. Some Leu-7 positive cells have only weak NK activity whilst the most efficient NK activity is associated with the Leu-11 positive subsets. Without using a two-colour double staining technique to demonstrate both Leu-7 and Leu-11 antigens simultaneously we are unable to determine the relative proportion of each of the subsets. The possibility remains that some of the Leu-7 positive cells are not NK cells as some natural suppressor cells also express the same antigen (Strober 1986).

Leu-7 and Leu-11 positive cells were found only in a minority of normal cervices in small numbers in the subepithelial stroma. In contrast, both Leu-7 positive and Leu-11 positive NK cells

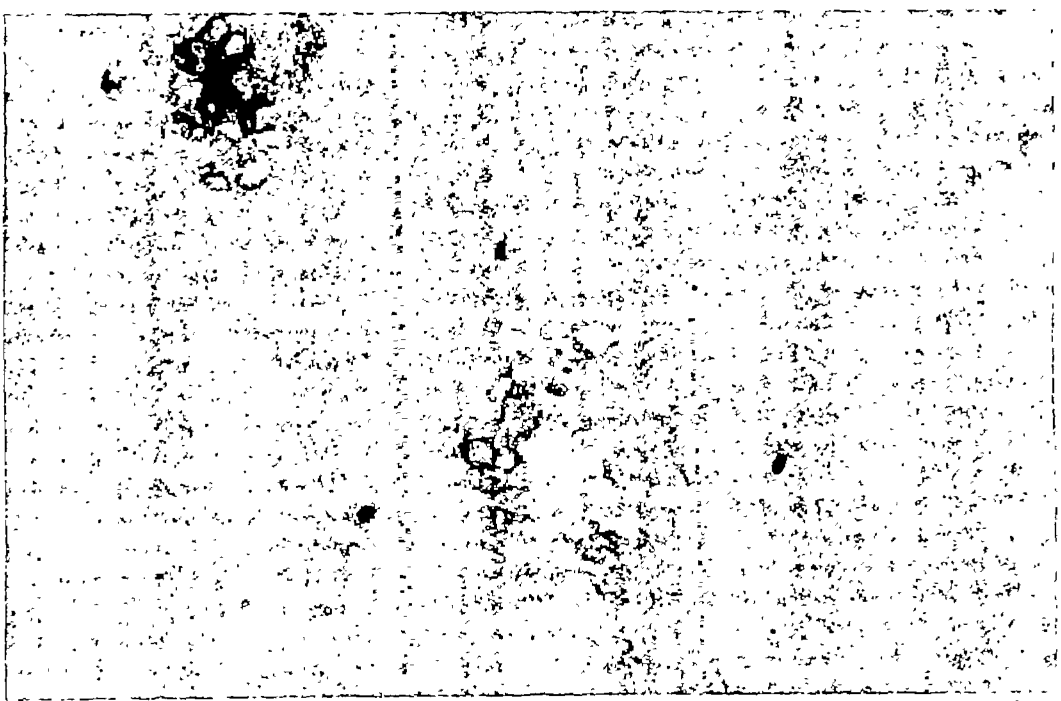

Fig. 2. Photomicrograph showing a moderate infiltration by Leu-11 positive NK cells in the stroma from a patient with simple HPV infection of the cervix. ×400.

were found in most HPV infections and in half the CIN specimens. The number of cells was usually small but two specimens showed a moderate and three a pronounced infiltration by Leu-11 positive cells. In three specimens Leu-11 positive cells alone were present. The presence of Leu-11 positive cells in these specimens suggests that these cells are likely to be NK cells.

The finding of NK cells in HPV infection without neoplasia indicates that HPV infection alone can trigger a NK cell response. However, the scanty presence of intraepithelial NK cells in HPV infection and CIN suggests that they are unlikely to be primarily involved in cytolysis of abnormal cells at the tumour site. This may be an example of a more generalized phenomenon as the number of NK cells in tumours is usually small (Moore 1985). It is not clear whether this is due to poor antigenicity of naturally arising tumours or a direct suppressive effect of tumour cells on NK cells.

Moore (1985) proposed that NK cells in lymphoreticular malignancies may be important in controlling the distribution of immature cells outside their normal anatomical compartments or spread of metastatic cells from such tumours into the peripheral blood circulation. In HPV infection and CIN, NK cells were found predominantly in the subepithelial stroma, suggesting that they may have a role in the prevention of the stromal invasion by HPV or neoplastic cells. However, the significance of these small numbers of NK cells in the progression of HPV infection and CIN, recurrence or development of invasive cancer remains to be elucidated.

NK cells have also been shown to secrete a wide range of lymphokines including interleukin-I (Kashara *et al.* 1983), interleukin-II (Scala *et al.* 1984), gamma interferon (Djeu *et al* 1982) and B-cell differentiation factor (Vyakarnam *et al.* 1985), suggesting a modulatory role in adaptive cell-mediated immunity. In HPV infection and CIN there is evidence of depletion of T-cells and Langerhans' cells (Tay *et al.* 1987*a*, 1987*b*) and a localized immune deficiency. The induction of the local immune suppression could be mediated via the immune modulatory lymphokines or suppression by the Leu-7 (HNK-1) positive cells

There was a marked individual variation in NK cell response. This was present in some but not other biopsies of HPV infection and CIN. Recently, Rees *et al* (1986) found that seminal fluid has a suppressive effect on NK activity. It is possible that frequent exposure to seminal fluid may reduce the optimal NK response to HPV

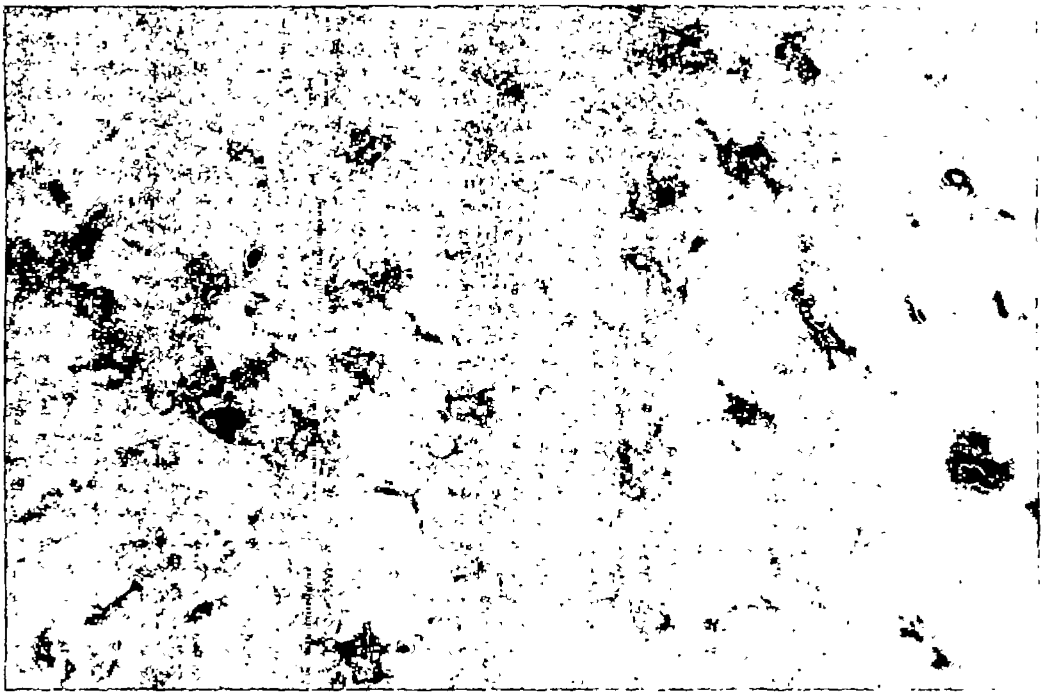

Fig. 3. Photomicrograph showing a pronounced infiltration by Leu-11 positive NK cells in the stroma from a patient with CIN 1. ×400

infection and CIN. Further investigations are needed to define the role of the small number of NK cells in the pathogenesis and progression of HPV infection and CIN.

Acknowledgment

We would like to thank Mr P. Maddox for his technical assistance and the Cancer Research Campaign, London for financial support.

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Received 29 September 1986
Accepted 17 December 1986

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 907–909

Doppler ultrasound features of stenosis of the aorta in a pregnancy complicated by Takayasu's arteritis. Case report

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Case report

A Mauritian woman aged 34 years, para 3+3, presented to the antenatal clinic with 6 weeks amenorrhoea. She had been hypertensive from the age of 18 years and investigations undertaken in Mauritius and Germany had revealed no apparent cause for the hypertension. She had been treated previously with alphamethyldopa 250 mg and prazosin 1 mg twice daily with good control of her blood pressure (prazosin had been discontinued on diagnosis of this pregnancy). The past obstetric history was poor. After a spontaneous miscarriage at 18 weeks, the next three pregnancies were undertaken with cervical ligatures *in situ*. Two liveborn children (one at term, and one at 32 weeks after 5 weeks hospitalization for hypertension) and an intrauterine death at 24 weeks resulted. After she migrated to Australia the patient had two further pregnancies both therapeutically terminated in the first trimester.

On examination she was 150 cm tall and weighed 57·5 kg. Her blood pressure (arm) was easily recorded at 130/80 mmHg and proteinuria was absent. There was a systolic ejection murmur at the left sternal edge and no evidence of cardiac failure. Femoral pulses were difficult to feel suggesting a diagnosis of coarctation of the aorta. Pelvic examination revealed a pregnant uterus consistent with dates. The cervix admitted a finger tip through the internal os and was 2 cm in length.

Routine antenatal testing showed the following: blood group O Rhesus positive with no antibodies present, haemoglobin 12·4 g/dl and a normal blood film. An ESR was not performed. Serology for syphilis was negative. The patient was rubella immune and the mid-stream urine analysis was negative. The blood urea was 4·9 mmol/l and creatinine was 66 μmol/l. An ultrasound scan at 9 weeks confirmed the dates. Antinuclear factor and lupus anticoagulant activity were negative. At 16 weeks a Macdonald cervical suture was inserted without complication. The patient was admitted to hospital for rest at 18 weeks with dyspnoea and a blood pressure of 140/90 mmHg (oxprenolol 80 mg three times daily was added). Maternal echocardiography at 19 weeks demonstrated a bicuspid aortic valve with no other abnormalities being seen. At 20 weeks hydralazine, 25 mg three times daily, was added to further control the blood pressure (160/100 mmHg). Renal function did not change during the pregnancy and creatinine clearance was 144 ml/min at 23 weeks.

Progress ultrasound scans at 20 and 24 weeks showed normal intrauterine growth. Renal and abdominal ultrasound revealed no apparent renal or abdominal pathology. Unexpectedly at 25 weeks and 4 days spontaneous rupture of the membranes occurred. Following removal of the suture the patient was given intramuscular betamethasone (12 mg twice 12 h apart). A repeat ultrasound showed a breech presentation with markedly decreased amniotic fluid. Serial fetal cardiotocography revealed no fetal compromise. Four days later the patient went into labour and was delivered by lower segment caesarean section through a vertical incision, of an 860 g male infant with Apgar scores of 2 and 7 at 1 and 5 min respectively. On discharge the infant was well without problems.

Before delivery an analysis was made of

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umbilical and uteroplacental artery flow velocity waveforms (Trudinger *et al.* 1985). The fetal umbilical artery waveforms were normal. The uteroplacental waveform analysis revealed a damping of the usual systolic acceleration seen in normal pregnancies (Fig. 1). This was also true for the femoral artery at its origin below the inguinal ligament which demonstrated a marked change in the velocity waveform. Instead of the usual flow profile with a rapid and short-lived systolic component and reversal of flow in diastole (Taylor *et al.* 1985), a slow sustained systolic rise with minimal diastolic reversal of flow was seen (Fig. 2).

After delivery the patient had aortic digital subtraction angiography and a renal radioisotope scan performed. The renal scan was unremarkable. The aortic digital subtraction angiography showed a long irregular stenosis of the aorta from the L1 to L4 level (Fig. 1) The intercostal arteries were dilated above the narrowing providing a collateral circulation. Stenosis was noted at the origin of the superior mesenteric artery (SMA) and both renal arteries. The middle colic branch of the SMA was dilated and supplied the branches of the inferior mesenteric artery (IMA) through the artery of Drummond. The IMA appeared to be obstructed at its origin. The pelvic and iliac arteries were normal in appearance. The aortic arch was normal. The findings were reported as being consistent with Takayasu's aortitis of the distal aorta.

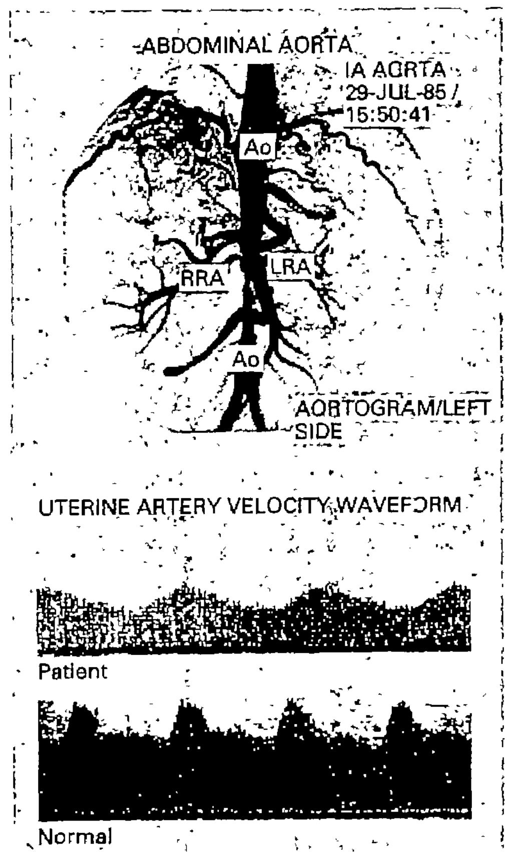

Fig. 1. Digital subfraction angiography and uteroplacental arterial velocity time waveforms in a patient with Takayasu's arteritis A waveform from a normal patient is included for comparison.

Discussion

Takayasu's syndrome is due to an arteritis of unknown aetiology occurring in the thoracic or abdominal aorta in young women. Histologically there is a chronic obliterative panarteritis causing disruption and fibrosis of the involved aorta and major arteries resulting in marked narrowing or even obstruction. The radiological diagnosis is dependent upon the demonstration of stenosis of the affected vessel with typical post-stenotic dilation. Although the histological findings of Takayasu's disease are well documented (Ishikawa & Matsuura 1982) the long-term prognosis is debatable. Previous authors have documented thoracic involvement of the aorta without pregnancy complications (de Jonge *et al.* 1983), but Ishikawa & Matsuura (1982) who reviewed a series of 85 pregnancies affected by this condition, described complications in the form of hypertension and heart failure in 60%.

In our patient we found abnormal uteroplacental artery Doppler ultrasound flow velocity waveforms which we believe to be diagnostic. The continuous wave Doppler ultrasound system described by Trudinger *et al.* (1985) was used to study the fetal umbilical placental circulation and the uteroplacental circulation. The fetal umbilical artery velocity waveforms were within normal limits, but maternal uteroplacental velocity arterial waveforms were strikingly different from those of a normal pregnancy. Although the continuing diastolic flow was very similar to that in normal pregnancy demonstrating low flow resistance, there was a delay in the upstroke of the velocity waveform in systole. The altered slope in systole is believed to be due to damping of the arterial pulsation as a result of the narrowing or stenosis of the aorta. A similar disturbance of the flow velocity waveform was observed when the femoral artery was studied.

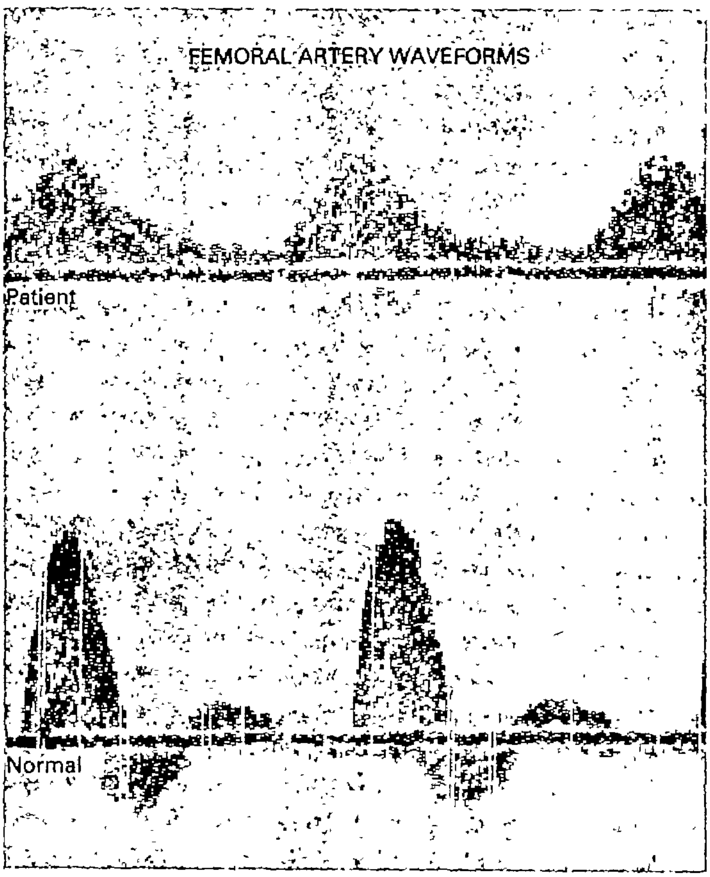

Fig. 2. Velocity time waveforms from the femoral artery in a patient with Takayasu's arteritis and a normal pregnant patient

This method of studying the uteroplacental circulation and femoral artery could be expected to show similar changes in aortic coarctation enabling the diagnosis of this condition to be made during pregnancy.

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Received 22 September 1986
Accepted 1 December 1986

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 910–914

A spectrum of postpartum thyroid disease. Case reports

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Case reports

Patient no. 1

The 32-year-old patient was delivered of a female infant in March 1982 after an uneventful first pregnancy. Postnatally for the first month she was well, though with profuse lactation. Over the next 2 months she gradually developed 'restlessness'. She was unable to sleep again after the night feed, was very tired but still active and was always hungry, despite which she was losing weight. She also suffered from sweating and palpitation. Pain and stiffness in her knees recurred, a problem that had resolved completely during her pregnancy. There was no other past history of note. There was no family history of thyroid disease; but her mother had 'rheumatism' and her father rheumatoid arthritis.

On examination, she was thin with a regular tachycardia. No goitre or bruit was found. Thyroid function tests (TFT) supported a diagnosis of mild hyperthyroidism (Table 1). As she was anxious to continue breast-feeding, no treatment was given, but TFT were repeated at intervals (Table 1).

Thyroid function declined rapidly over the next few weeks until the patient was frankly hypothyroid (T_4 46 nmol/l, TSH 31·2 mU/l) and feeling extremely tired. Since earlier reports indicated that spontaneous improvement was likely to occur, she was not given any treatment, but her family doctor was invited to initiate thyroxine therapy if overt symptoms of hypothyroidism developed.

She gradually improved until by the end of 1982 (9 months later) she was feeling well and TFT were normal.

She was seen again a year later when she was pregnant for the second time. TFT at 17 weeks gestation were normal (Table 1). She remained extremely well throughout the pregnancy and postpartum period. TFT were repeated 3 months postpartum and were normal. At no time did she have any subjective evidence of thyroid dysfunction during the year following her second delivery.

Patient no. 2

The patient, aged 22, presented to her family doctor 3 months postpartum because of excessive tiredness and weight gain in spite of a poor appetite. She had been delivered of a male infant in October 1982 at full term after induction for mild pre-eclampsia. Examination revealed a small goitre, and thyroid function tests showed her to be markedly hypothyroid (Table 2). There was no relevant past medical or family history.

Because of these abnormal results, she was followed up in the endocrine clinic. At no time was she given any therapy but both clinically and biochemically she gradually improved, until by October 1983 (9 months later) she was euthyroid (Table 2).

It is interesting to note that microsomal antithyroid antibodies were present on both occasions that they were measured, the titre falling with clinical improvement.

She was seen again in June 1984 as she was pregnant for a second time. TFT at 8 weeks gestation were normal apart from minimal elevation of TSH which was not confirmed at 12 weeks. The patient gave birth to a female infant in December 1984 at 36 weeks, and at 3 months postpartum she was clinically and biochemically euthyroid with normal TFT (Table 2)

During the next month she demonstrated a very precipitous change in thyroid function,

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Table 1. Thyroid function tests in patient 1 in relation to two pregnancies

Date	T_4 (60–140) (nmol/l)	FT_4 (9–22) (pmol/l)	T_3 (0·8–2·5) (nmol/l)	TSH (<5) (mU/l)	TBg (7–17) (mg/l)	Thyroid microsomal antibodies	Comments
First pregnancy							
Before referral	172	63	2·6	—	—	—	Approximately 2 months postpartum
3/6/82	98	30	2·0	2·1	7·6	—	3 months postpartum
21/6/82	53	12·6	1·0	1·2	—	—	—
27/6/82	46	8·1	1·3	31·2	—	—	Very tired
13/9/82	57	10·4	2·0	16·5	9·4	160^2	—
13/12/82	60	10·9	1·5	5·4	—	—	Well
Second pregnancy							
28/11/83	107	10·9	—	2·1	13·9	20^2	17 weeks pregnant
10/2/84	98	—	—	2·1	—	—	—
30/4/84	123	—	2·6	3·3	—	—	10 days postpartum
13/7/84	142	28 (8–30)	2·2	—	—	—	3 months postpartum

T_4, Thyroxine; FT_4, free thyroxine, T_3, triiodothyronine; TSH, thyroid stimulating hormone; TBg, thyroxine binding globulin.

Reference ranges are shown in brackets at the head of each column. The last tests were performed elsewhere and the reference range for FT_4 was 8–30 pmol/l.

becoming once again markedly hypothyroid. This time she was treated with thyroxine and TFT returned to normal. She is taking 150 μg thyroxine daily, but despite apparently satisfactory control she remains unwell, complaining of excessive tiredness which makes it difficult to cope with the ordinary demands of family life.

Patient no. 3

This 28-year-old patient gave birth to her first child in October 1975. Ten months later in April 1976 she developed thyrotoxicosis and was treated with carbimazole for 5 months until she was euthyroid. A second, and worse attack developed in May 1978 and she was treated with carbimazole for 18 months until January 1980, after which she remained well.

In November 1981 she gave birth to her second child and was well again for the first few months until at 8 months postpartum she developed symptoms of thyrotoxicosis. She had lost 6·4 kg in weight, developed a tremor and tachycardia (100/min). She was started on propranolol, 10 mg three times daily, by her general practitioner and referred to the endocrine clinic, where she was seen 6 weeks later. By this time she was feeling much better, she had gained weight and was not obviously thyrotoxic, although a small goitre was palpable but with no bruit. Her pulse rate was 76/min and regular This episode of thyrotoxicosis had obviously been very transient, as was confirmed by the low-normal TFT (Table 3). Repeat tests 4 weeks later were normal and propranolol therapy was reduced gradually and stopped.

She remained well and euthyroid until January 1984 when, following an exhausting time with an active infant, she developed further symptoms. Initially she noticed that she was unable to 'keep a note when singing' and that her handwriting had altered. She then started to lose weight, developed palpitation, breathlessness and nervousness. TFT showed T_4 250 nmol/l, T_3 >10 nmol/l and FT_4 >120 pmol/l. She was treated with carbimazole and propranolol for 13 months until euthyroid, when therapy was stopped and since then she has remained well.

It is of interest that the patient's grandmother had developed severe thyrotoxicosis during the menopause at 50 years of age in the early 1930s. She was bed-ridden for 3 years until she recovered and lived to be 81 years of age.

Discussion

Pregnancy-related thyroid disease is well recognized, especially that caused by autoimmunity.

Table 2. Thyroid function tests in patient 2 in relation to two pregnancies

Date	T_4 (60–140) (nmol/l)	FT_4 (9–22) (pmol/l)	TSH (<5) (mU/l)	Microsomal antibodies	Comments
First pregnancy					
13/1/83	21	—	90	—	3 months postpartum
7/2/83	93	8·3	29·3	320^2	
21/2/83	113	12·8	14·5	—	
18/4/83	120	13·2	8·3	80^2	
3/10/83	111	—	3·4	—	Discharged well
Second pregnancy					
14/5/84	90	—	9·0	—	8 weeks pregnant
11/6/84	145	—	4·5	—	12 weeks pregnant
4/3/85	89	—	1·2	—	3 months postpartum
1/4/85	37	—	50	—	
7/6/85	150	—	1·0	—	On thyroxine replacement therapy

Reference ranges are shown in brackets at the head of each column.

A wide spectrum of thyroid disorders may occur, particularly in the first year after delivery (Amino *et al.* 1982*b*). This can vary from transient to persistent hypothyroidism, transient hyperthyroidism or aggravation of known Graves' disease. Our three patients illustrate three aspects of this spectrum.

Many autoimmune diseases such as SLE (Friedman & Rutherford 1956), rheumatoid arthritis (Oka 1953), goitrous hypothyroidism (Nelson & Palmer 1975) and Graves' disease (Gardiner-Hill 1929; Amino *et al.* 1977*b*) may ameliorate during pregnancy and relapse in the postpartum period. It is suggested that the immunosuppresive effect associated with pregnancy results in remission and after delivery a rebound phenomenon causes a transient worsening of the disorders (Walfish & Chan 1985).

Immunological changes have been shown to occur during pregnancy and after delivery. Amino *et al.* (1978) have observed a gradual decrease in serum antithyroid antibodies during pregnancy followed by a striking, but transient increase in the titre postpartum. Amino *et al.* (1982*b*) suggest that women who are immunologically predisposed to thyroid antibody formation are particularly prone to develop abnormalities of thyroid function, both hypo- and hyperthyroidism, in the postpartum period. The syndromes found as a result of the aggravation of subclinical autoimmune thyroid disease seem to cover a wide spectrum in which they blend one with another with a complexity that makes precise differentiation impossible.

Postpartum thyroiditis leads to transient hypothyroidism, which may or may not be preceded by a short episode of hyperthyroidism. Amino *et al.* (1976, 1977*a*) initially reported a number of such patients in Japan and others have been reported in various countries; Jansson *et al.* (1984*a*) found a similarly high prevalence in Sweden. Our first two patients illustrate this disorder.

In patient no. 1 hypothyroidism was preceded by a short spell of hyperthyroidism; recovery was spontaneous without any treatment, and there was no recurrence of symptoms after a second pregnancy. The absence of a palpable goitre adds particular support to the diagnosis of

Table 3. Thyroid function tests 8 months after delivery in patient 3

Date	T_4 (60–140) (nmol/l)	FT_4 (9–22) (pmol/l)	T_3 (0·8–2·5) (nmol/l)	TSH (<5) (mU/l)	Thyroid microsomal antibodies	Comments
4/10/82	62	8·4	1·4	2·0	80^2	On referral
8/11/82	76	10·2	2·1	2·0	—	Propranolol gradually reduced

Reference ranges shown in brackets at the head of each column. For abbreviations see Table 1.

the transient nature of the thyrotoxicosis. Many of the cases described with this syndrome lack thyroid enlargement (Amino *et al.* 1982*b*) unlike that found in Graves' disease. Also of interest was the amelioration of arthritis during pregnancy followed by its worsening postpartum. Despite the family history of rheumatoid arthritis, the patient had no positive diagnosis of arthritis. She was seen by a rheumatologist 2 years before the first pregnancy; at that time the ESR was 10 mm/h, rheumatoid factor was negative and interestingly, thyroid antibodies were positive.

Our second patient illustrates the development of severe hypothyroidism after two successive pregnancies, without any evidence of a thyrotoxic phase. She recovered spontaneously from the first episode without any treatment, but needed replacement therapy with thyroxine after the second pregnancy, on which she still remains. The stress of family life with two small children made it impossible to wait for spontaneous resolution of the hypothyroidism on this second occasion. It is intended to reduce the dose of thyroxine, and to withdraw it altogether at a later date.

Amino *et al.* (1982*b*) found a prevalence of postpartum primary hypothyroidism of 3·0% in Japan with only 0·2% becoming persistently hypothyroid, this may have occurred in our second patient.

Postnatally, established Graves' disease may relapse or overt Graves' disease may appear for the first time (Walfish & Chan 1985) as in our third patient with known Graves' disease who had two pregnancies during the recurring course of this disorder. The second pregnancy was followed by a transient attack of thyrotoxicosis that responded to propranolol alone.

Amino *et al.* (1982*a*) have shown that patients with Graves' disease, who are in remission and on no medication, have an increased FT_4 index in the first trimester of pregnancy, which returns to normal in the second and third trimester. They also showed that patients with a particularly high FT_4 early in pregnancy were more likely to relapse postpartum. FT_4 index correlates well with FT_4 levels which is the test more commonly used (Jansson *et al.* 1984*b*).

There is now considerable evidence that thyroid disease may be an important cause of morbidity in the postpartum period. Transient thyroiditis is a well documented, but poorly recognized, syndrome which may be easily overlooked and the associated tiredness and depression ascribed to the demands made on the mother at this time.

We conclude that any patient presenting with such symptoms in the first year after delivery should have laboratory tests of thyroid function, particularly patients known to have thyroid antibodies. If hypothyroidism is discovered treatment may not be required as spontaneous recovery usually occurs, but reassurance and follow-up are essential. The ultimate prognosis in these patients, most of whom have thyroid antibodies, is not known.

Acknowledgment

We are grateful to Professor H. S. Jacobs for permission to publish these cases which are under his care, and for his interest and advice.

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Received 22 December 1986
Accepted 29 April 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 915–916

SHORT COMMUNICATIONS

The importance of a slit-like lumen cross-section for the mechanical function of the cervix

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The primary function of the cervix is mechanical: it remains closed to maintain the fetus within the uterus until parturition when it dilates to allow delivery. The cervix may be considered, very simply, as a tube connecting the uterus to the vagina. In considering the mechanical behaviour of a tube it is the cross-sectional shape of the lumen and the stiffness of the walls that determine the way in which it functions. Though frequent mention is made of the stiffness of cervical tissue, and the dramatic softening that takes place at parturition, the importance of lumen cross-section for maintaining the closure of the cervical canal appears to have been overlooked. To maintain this closure by muscular activity seems unlikely as there is only a small amount of muscle present (Danforth 1947; Rorie & Newton 1967). Furthermore it would require continuous expenditure of energy.

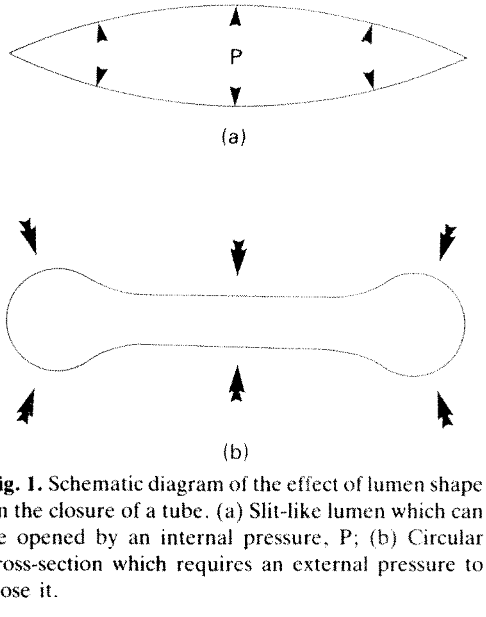

Fig. 1. Schematic diagram of the effect of lumen shape on the closure of a tube. (a) Slit-like lumen which can be opened by an internal pressure, P; (b) Circular cross-section which requires an external pressure to close it.

Anatomy

The shape of the human cervical canal is traditionally described as 'somewhat fusiform, flattened from before backwards' (e.g. Singer & Jordan 1976); when the cervix is sectioned in a frontal plane it appears spindle shaped, broadest in the middle and narrowing towards the ends, and in a sagittal plane it appears straight (Danforth 1983). That description suggests that the lumen cross-section in the plane perpendicular to those above, i.e. a transverse section, is slit-like. This slit-like cross-section is clearly demonstrated in published drawings and photographs of human cervices (Danforth 1983) though this point is rarely made explicitly. The lumen cross-section may be irregular or branched but the important aspect of the shape is that it is narrow and slit-like and in no way circular. This slit-like cross-section of the canal leads to a tube that is closed when relaxed.

Closure mechanism

A tube with a circular cross-section, if compressed, will tend to pass through a shape such as that shown schematically in Fig. 1b when partially closed; further pressure will complete the closure of the central region but leave the two outer regions still open (Kresch 1979). To close these requires a considerably greater pressure as the flexural stiffness of the walls increases rapidly with curvature. The work done in compressing the tube is stored as energy in the increased curvature of the walls. On releasing the pressure the tube will open to reduce the curvature of the walls thereby reducing the energy stored in them. In contrast, a flat tube with a slit-like cross-section (Fig. 1a) will remain closed if the pressure inside is equal to that outside. The lumen will open if the internal pressure is increased (Fig. 1a) but will close again as soon as the pressure is removed.

The slit-like lumen of the cervix means that it remains closed with no expenditure of muscular effort. Opening is promoted by increasing the internal pressure. A similar mechanism has been reported for the retention of urine by the urethra which also has a slit-like lumen cross-section (Pullan *et al.* 1982).

Acknowledgment

I thank the Medical Research Council for support.

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Received 5 February 1987
Accepted 16 June 1987

British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 917–920

BLAIR BELL RESEARCH SOCIETY

Papers presented at the joint meeting with the British Fertility Society on 11 December 1986 at the Royal College of Obstetricians and Gynaecologists

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Patterns of luteinizing hormone (LH) secretion in normal and oligozoospermic men by N. F. Perks, A. P. Murdoch, M. C. White, T. F. Cox & W. Dunlop. Department of Obstetrics and Gynaecology, University of Newcastle upon Tyne

The pathogenesis of oligozoospermia is largely unexplained. It appears that follicle stimulating hormone (FSH) is necessary for the initiation of spermatogenesis in men but that luteinizing hormone (LH) alone is required for its maintenance. Agents that increase the concentrations of gonadotrophins have been used to treat men with idiopathic oligozoospermia. Although the pattern of LH secretion in oligozoospermic men has not been investigated previously, some disorders of ovulation in women are associated with abnormal pulsatile LH secretion. Recent studies from Newcastle upon Tyne have demonstrated the presence in normal women of small pulses of fast frequency superimposed upon larger, slower pulses. We have extended these studies to normal and oligozoospermic men. Venous samples were collected from eight normal and eight oligozoospermic men at 1-min intervals for 1 h and at 5- or 10-min intervals for a further 5 h. The concentration of LH was determined in all samples by radioimmunoassay and the results subjected to spectral analysis. Mean LH concentrations were 4·4 (SD 1·0) i.u./l and 5·5 (SD 1·3) i.u./l in the normal and oligozoospermic groups. Mean corresponding FSH concentrations were 3·6 (SD 1·8) i.u./l and 5·3 (SD 2·9) i.u./l respectively and mean corresponding testosterone concentrations 18·7 (SD 4·2) nmol/l and 20·7 (SD 6·9) respectively. Differences in basal LH, FSH and testosterone concentrations between the two groups were not statistically significant. Normal men had a pulsatile pattern of LH concentration that varied in frequency from 80 to 180 min (mean 122 min); mean pulse amplitude was 2·5 (SD 1·1) i.u./l. The oligozoospermic men also showed a pulsatile pattern of LH concentration. Pulse frequency varied between 60 and 180 min (mean 114 min); mean pulse amplitude was 2·8 (SD 1·0) i.u./l. In addition both groups showed pulses of smaller amplitude in the frequency range of 5–20 min superimposed upon the major pulse pattern. We suggest that LH secretion is normal in oligozoospermic men and that the underlying pathophysiology is more likely to be at gonadal than at hypothalamic/pituitary level. In view of this, the rationale for using agents that raise LH concentration to treat oligozoospermic men needs to be reconsidered.

A comparative study of an LHRH agonist (buserelin) and danazol in the treatment of endometriosis by W. Matta, R. W. Shaw, G. Burford & A. Kirkland. Academic Department of Obstetrics and Gynaecology, Royal Free Hospital, London NW3

The realization that repeated administration of LHRH agonists induces suppression of the hypophyseal-pituitary-ovarian axis and hypo-oestrogenism (medical oophorectomy) suggested a new approach in the treatment of endometriosis. Sixty-one patients with endometriosis confirmed and staged (revised AFS classification) at laparoscopy were allocated by random number to either danazol (Winthrop Laboratories, Guildford, Surrey) ($n = 20$), 400–800 mg daily, or buserelin (Hoechs-Roussell, USA) ($n = 41$), 400 µg three times daily, intranasally. Treatment continued for 6 months with follow-up for a minimum of 6 months. A second laparoscopic assessment was made at the end of treatment. Clinical and endocrine assessments were made monthly. After 3 months of treatment mean plasma oestradiol levels were lower in the buserelin group (92 pmol/l) than in the danazol group (165 pmol/l). Overall cure rates were 82% in the buserelin group and 72% in the danazol groups. Both groups experienced statistically significant symptomatic relief whilst on treatment. There was a higher incidence of side-effects in the danazol group.

The suppression of the mitogenic response to phytohaemagglutinin by placental protein 14 (PP14) by A. G. Pockley, E. A. Mowles*, R. J. Stoker*, O. M. R. Westwood†, M. G. Chapman† & A. E. Bolton. Departments of Biological Sciences, Sheffield City Polytechnic and *North East London Polytechnic, and †Obstetrics and Gynaecology, Guy's Hospital, London

A variety of mechanisms have been proposed to explain the survival of the semi-allogeneic fetus during pregnancy; during implantation and early pregnancy a localized immunosuppressive activity may be of particular importance. We have investigated decidual tissue for such activity. Extracts of decidual tissue sampled at 14 weeks gestation were assessed for their effects on the lymphoproliferative response to phytohaemagglutinin (PHA). Lymphocyte cultures incubated with crude decidual extracts containing up to 13·3 mg/l of placental protein 14 (PP14), measured by radioimmunoassay, suppressed the mitogenic response to PHA by 55% compared to control cultures. The immunosuppressive activity of the decidual extracts was closely related to their PP14 content over the range investigated (0–13·3 mg/l PP14). Addition of the decidual extract after culturing lymphocytes with PHA for 36 h produced maximal inhibition, indicating the suppression of previously activated cells. Following the treatment of the decidual extracts with monoclonal anti-PP14 immunoadsorbant, which reduced their PP14 content as measured by radioimmunoassay and two-dimensional crossed immunoelectrophoresis, the observed suppression of the lymphoproliferative response was reduced in parallel to the reduction in PP14 concentration. These findings indicate that PP14, which comprises some 5–10% of the total soluble protein content of decidual tissue, has an immunosuppressive activity which may be important for the survival of the implanting embryo and for maintenance of early pregnancy.

Teratogenicity of serum from patients with histories of recurrent miscarriages using an in-vitro whole embryo culture technique by M. Anwar, F. Beck* & J. MacVicar. Departments of *Anatomy and Obstetrics & Gynaecology, University of Leicester Medical School, Leicester LE1 7RH

Post-implantation rat embryos can be grown successfully in immediately centrifuged, heat-inactivated and appropriately supplemented normal human serum using a roller culture method. Since embryonic growth and development from pre-somite to 25-somite stages is similar to that obtained *in vivo*, this method provides an opportunity to investigate human sera for potential embryopathy over much of the period of organogenesis. Using this technique, sera from 12 women with histories of recurrent miscarriage was investigated. Control samples were obtained from appropriately matched individuals. Samples of sera from women with histories of recurrent miscarriage adversely affected embryonic growth and differentiation as assessed by a morphological scoring system and by their total protein content. Embryos grown in sera from three of these women exhibited abnormalities of neural tube closure and of optic and otic systems more frequently than the embryos grown in sera from the other nine.

Human chorionic gonadotrophin (hCG) metabolism in ovulatory women by N. C. Sharp, F. Anthony, J. F. Miller & G. M. Masson. Human Reproduction and Obstetrics, University of Southampton

Dosage schedules for hCG induction of ovulation tend to be empirical. We studied hCG metabolism in patients receiving hCG for ovulatory purposes and found a variation in the excretion patterns of hCG after intramuscular injection. Seven patients were studied during a total of 16 cycles. Sera and early morning urine samples were collected daily for 7 days after injection. In 10 of these cycles (three patients) the total urine voided in the first 24 h after injection was collected and the amount of excreted hCG calculated. Creatinine values were also measured in three of the 24-h collections (one from each of the patients) and the creatinine clearances calculated. All patients except one had hCG levels <50 i.u. in sera and urine by the seventh day after 10 000 i.u. had been given although the 'decay curves' did not follow a uniform pattern. One patient, however, had levels of 200 i.u. hCG in serum on day 7 after 10 000 i.u. and 165 i.u. hCG after 5000 i.u. Even after a dose reduction to 1250 i.u. the serum level on day 7 was 51 i.u. This patient surprisingly excreted between 9·5% and 17·1% of the total administered dose in the first 24 h, the excretion rate being related to the dose. The best excretion rate achieved by the other two patients was 5·8% (after 10 000 i.u.). These differences showed no correlation with the creatinine clearances. The fact that this individual had persistently high serum levels but a high renal excretion rate suggests that she was able to mobilize the hCG more quickly and more completely from the injection site, which was in keeping with her slight build and athletic pursuits.

Luteal deficiency and unexplained infertility: diagnosis and treatment by C. M. A. Glazener, C. Coulson, P. A. Lambert, E. M. Watt, R. A. Hinton, N. J. Kelly & M. G. R. Hull. University Department of Obstetrics and Gynaecology, University of Bristol, Bristol Maternity Hospital BS2 8EG

Conception rarely, if ever, occurs in cycles with inadequate luteal progesterone levels. The occurrence of such subfertile cycles in infertile women has simply been taken as evidence of their causal importance in diagnosis, but this has never been proven. We compared mid-luteal serum progesterone levels in 159 women with unexplained infertility with those in 58 normal controls. There were no significant differences in terms of mean progesterone values (41 compared with 44 nmol/l); frequency of defective cycles (progesterone <28 nmol/l: 17% compared with 15%); frequency of a clinical diagnosis of luteal deficiency (based on at least two of three cycles being defective: 13% compared with 12%); or persistent luteal deficiency (based on a second series being defective: 8% compared with 7%). Overall, only 1·7% of infertile patients and 4·9% of controls had evidence of persistent luteal deficiency. These findings suggest that defective cycles occur as a random phenomenon in normal as often as in infertile women, and luteal deficiency is a doubtful clinical entity of little relevance. We also examined the benefit of clomiphene treatment of unexplained infertility by randomized placebo-controlled crossover study in 118 patients. Compared with placebo, clomiphene led to a 66% increase in mid-luteal serum progesterone levels (from a mean of 43 nmol/l to 71 nmol/l, $P<0{\cdot}001$) and a 53% rise in the 3-month cumulative conception rate from 14·6% to 22·3% ($P<0{\cdot}05$). We conclude that clomiphene is of benefit in unexplained infertility but that this is not due to treatment of overt or occult luteal deficiency.

A comparison of abdominal mechanical sector ultrasound with vaginal mechanical sector ultrasound in monitoring follicular growth and development during natural and clomid cycles by R. K. Goswamy, G. Williams, C. Howles, M. Macnamee, R. G. Edwards & P. C. Steptoe. Bourn Hall Clinic, Bourn Hall, Bourn, Cambridge CB3 7TR

Abdominal and vaginal ultrasound monitoring of follicular growth was compared in patients attending Bourn Hall for frozen embryo replacement cycles. Abdominal ultrasound has been used widely for monitoring follicular growth, but, for adequate display of follicles, patients must have a full bladder which can often be extremely uncomfortable. Abdominal scarring and pelvic scarring can result in poor imaging. These problems seem to be overcome by the use of vaginal ultrasound. All patients attending were scanned per abdomen by one observer and then scanned again the same day vaginally by another observer unaware of the abdominal findings. Data from 20 patients indicate that the two methods provide a good correlation in follicular size and endocrine profiles ($r = 0{\cdot}93$).

The effect of increased abnormal sperm morphology on the outcome of in-vitro fertilization by S. Avery, H. Goodall, V. Marriott & B. Mason. The Hallam Medical Centre, 77 Hallam Street, London W1N 5LR

It has been suggested that high levels of morphologically abnormal sperm are associated with reduced rates of embryo growth and reduced embryo quality, but not with reduced fertilization rates. In this study of 250 cases, a trend was observed indicating a decrease in fertilization with increasing abnormal sperm morphology. In patients for whom tubal damage was the only indication for IVF a difference of 32% was observed in the fertilization rates between those whose levels of abnormal morphology were above the mean and those whose levels fell below it. A comparison of embryo growth rates between these two groups showed no significant difference. No association was found between embryo quality and increased levels of abnormal sperm, suggesting that once fertilization has occurred, increased abnormal sperm morphology has no apparent influence on embryo development.

Translaparoscopic salpingoscopy by I. Brosens. Department of Obstetrics and Gynaecology, University of Leuven, B-3000 Leuven, Belgium

Endoscopy of the fallopian tube allows detailed examination of the mucosa of the ampullary segment in subfertile patients. The present study describes the use of a rigid 2·6 mm telescope (salpingoscope) passed along the channel of the operative laparoscope to assess the mucosa up to 4–5 cm in the ampullary segment. The new technique was assessed in a series of 120 patients with infertility and 25 control patients. The ampullary segment was accessible for the salpingoscope in 92% of the patients. No major complications occurred. Lesions were detected in patients with apparently normal tubes on the hysterosalpingogram (HSG) and at laparoscopy. The ampullary mucosa was assessed in patients with tubocornual blocks and hydrosalpinges before laparotomy. In 21 hydrosalpinges the HSG showed preservation of the ampullary folds but salpingoscopy revealed focal or extensive lesions of the mucosa in 10 (48%) and in 17 hydrosalpinges the fold pattern appeared abnormal on the HSG but was normal at salpingoscopy in 6 (35%). In the presence of a tubocornual block, salpingoscopy is the only method to assess the ampullary segment. Salpingoscopy is superior to HSG in the assessment of the ampullary segment of the fallopian tube and is proposed as a useful new tool in the selection of patients for microsurgery, IVF or GIFT (gamete intra-fallopian transfer).

Early experience with the GIFT (gamete intra-fallopian transfer) procedure in the treatment of infertility by D. Lim-Howe, A. Wong, M. Dooley, M. Savvas, P. Turner, P. Stocker & J. Studd. Fertility and Endocrinology Centre, Lister Hospital, London SW1W 8RH

Fourteen patients were treated with GIFT. The mean age of the patients was 33·4 years (range 23–41 years) and the mean duration of infertility was 5·4 years (range 1·5–10 years). Infertility was due to a male factor in four couples, due to endometriosis in one and polycystic ovarian syndrome in another and unexplained in the remaining eight. In all but one patient clomiphene citrate and pergonal (human menopausal gonadotrophin) was used to induce superovulation. Buserelin was used in combination with pergonal in the patient with polycystic ovarian disease. Serial ultrasound was used to monitor response and to time hMG administration. Laparoscopic egg recovery and GIFT was performed 32–34 h after intramuscular administration of 7500 i.u. of hMG. There were five singleton pregnancies initiated in the 14 cycles (35% pregnancy rate). One spontaneous miscarriage occurred at 13 weeks and no pregnancy has yet gone to term. GIFT appears to be more successful than IVF in the treatment of unexplained and male infertility. The optimum number of oocytes and the minimal number of viable sperm to be transferred for a successful outcome has yet to be defined.

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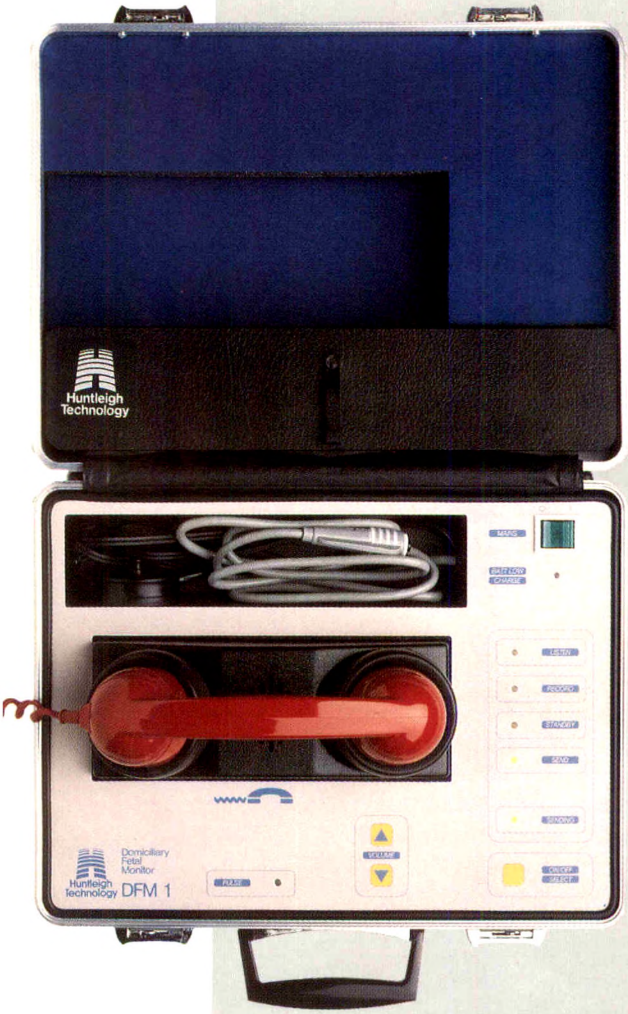

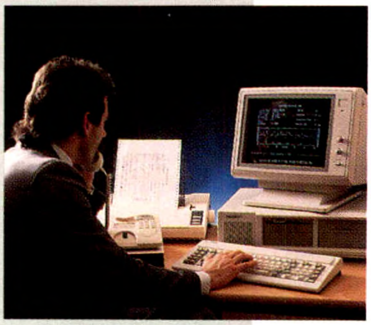

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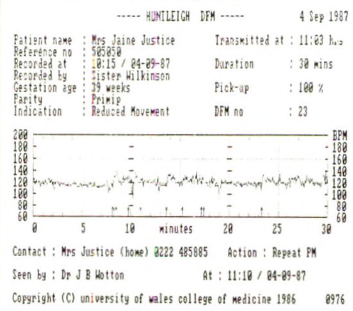

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----- HUNTLEIGH  DFM -----                 4 Sep 1987

Patient name   : Mrs Jaine Justice     Transmitted at : 11:03 hrs
Reference no   : 505050
Recorded at    : 10:15 / 04-09-87      Duration       : 30 mins
Recorded by    : Sister Wilkinson
Gestation age  : 39 weeks              Pick-up        : 100 %
Parity         : Primip
Indication     : Reduced Movement      DFM no         : 23

Contact : Mrs Justice (home) 0222 485885   Action : Repeat PM

Seen by : Dr J B Wotton              At : 11:10 / 04-09-87

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September 1987, Vol. 94, pp. 921–925

CORRESPONDENCE

Vaginal and abdominal delivery increases maternal urinary 6-keto-prostaglandin $F_{1\alpha}$ excretion

In April 1987 we published a letter from J.Y. Jermey *et al.* commenting on the above paper by Ylikorkala *et al.* [*Br J Obstet Gynaecol* (1986) **93,** 950–954]. The authors have now replied.

Authors' reply

Dear Sir,

In reply to Jeremy *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 376–378], we reported progressive rises in maternal urinary 6-oxo-$PGF_{1\alpha}$ during vaginal delivery (about 5·5 times the initial level) and caesarean section (about 65 times the initial level). We speculated that these changes could have originated 'from the maternal vascular bed, kidneys, or the myometrium and/or intrauterine tissues which are all capable of producing PGI_2 *in vitro*'. We then continued '. . . because the manipulation and traumatization of the myometrium and intrauterine tissues is more extensive during caesarean section than vaginal delivery, the higher . . .'

Dr Jeremy and his colleagues seem to be disappointed that we did not discuss the elevations in catecholamines and non-esterified fatty acids (NEFA) as a possible reason for PGI_2 rise. Every obstetrician knows that almost everything in female physiology reacts to labour and caesarean section. If catecholamines and NEFA had been discussed, then steroid hormones, neurohypophyseal hormones, opiates, prolactin etc, etc, should also have been included because the concentrations of all of them change during labour and they have been connected to prostanoids. We considered this kind of discussion too speculative, particularly since we measured none of the above mentioned agents.

The claim that we did not mention trauma as a possible mechanism of PGI_2 rise must result from inaccurate reading of our paper because we did discuss this possibility, as is clear from a paragraph cited above.

We did not refer to Jeremy *et al.* (1984*a*) because this rather unknown journal was not available to us, and the work of Ritter *et al.* (1986) was published after our manuscript was submitted. Furthermore, it is not self-evident that the comparisons with the data from animals or nonpregnant subjects are relevant at all in this context. Indeed, we did not even refer to our own work on PGI_2 rise in nonpregnant subjects undergoing heart surgery (Ylikorkala *et al.* 1981).

We agree that data on urinary thromboxane A_2 would have been of interest but we could not supply data which we did not have.

The patients undergoing caesarean section are routinely catheterized. Thus, no bladder distension was present. However, we appreciate the point that the urinary tract may contribute to urinary 6-oxo-PGI_1 in pregnant women, as it seems to do in nonpregnant rats (Jeremy *et al.* 1984*b*). The other data from Jeremy *et al.* (1987) were not yet published and therefore we could not refer to them.

The ranges and even the individual data can be read easily in Figures 1 and 2 of our article. We tested the changes of each individual by the paired *t*-test, which is the test of choice in this context. The changes were so huge that there can be no doubt about their significance.

We thank Dr Jeremy and his colleagues for their interesting comments. We appreciate their excellent contributions on prostanoids. Unfortunately, for the reasons discussed above, we were unable to refer to them in our paper but we hope that this correspondence has remedied this omission.

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The night—a dangerous time to be born?

Dear Sir,

I read with interest this article from Switzerland by Domenighetti & Paccaud [*Br J Obstet Gynaecol* (1986) **93**, 1262–1267]. There seemed to be something very strange about the population described. The ratio of the number of births for each hour of the day (Fig. 1, their article) shows an unusual pattern with an increase

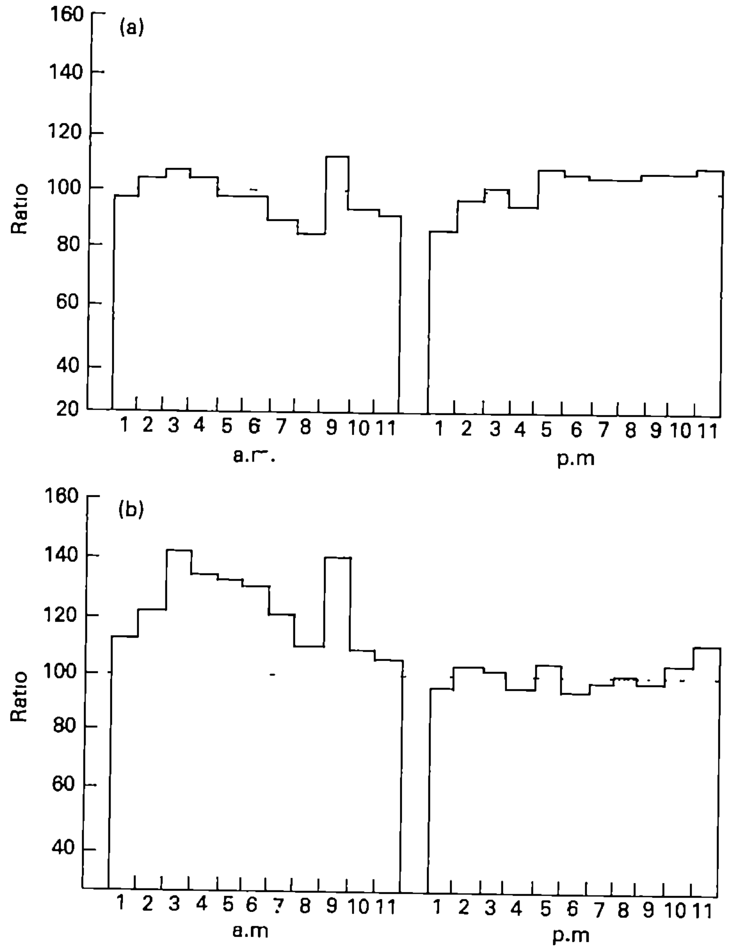

Fig. 1. Observed to expected ratios of birth numbers by hour of day recalculated from *British Births 1970* (Chamberlain *et al* 1978). (a) All singleton births (n = 16 815), (b) Singleton births excluding caesarean section, induction and augmentation (n = 11 875).

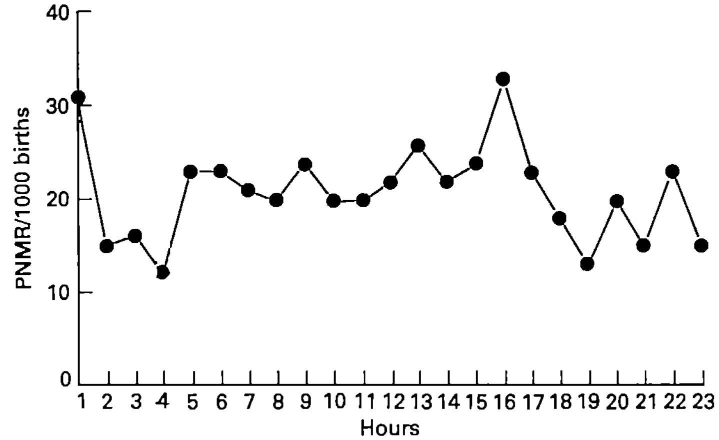

Fig. 2. Perinatal mortality ratios per thousand singleton total births from *British Births 1970* (Chamberlain *et al.* 1978) (*n* = 16 815).

between 07·00 and 14·00 hours. This is different from most of the Western World where the bulge is usually in the early hours of the morning.

I went back to the National Birthday Trust British Births 1970 study (Chamberlain *et al.* 1978) which reported 16 815 singleton births in one week. Recalculating data from this shows a ratio of observed to expected births by hour of day illustrated in Fig. 1a. In case medical intervention had altered the proportions, those women who had caesarean section (757), were induced (4387) and 231 women whose labour was augmented were excluded; the remaining 11 875 produced ratios shown in Fig. 1b, which are close to those produced from many other studies. More germanely, the perinatal mortality rate of the whole group by hour of day is shown in Fig. 2. There is no correlation with the time of day and the changes seen in the Swiss study are not confirmed.

Perhaps the differences are due more to the population served than to the poor staffing levels as Domenighetti & Paccaud contend. Some 18·4% of their study population was delivered by caesarean section and an unquoted number after induction. This probably accounts for the bulge between 07·00 and 14·00 hours, thus leaving a group of those apparently having fewer interventional procedures in the other hours.

To conclude that lower staff levels are an explanation is too hypothetical unless staff levels are documented, described and correlated to events in the labour wards.

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Domenighetti, G. & Paccaud, F. (1986) The night—a dangerous time to be born? *Br J Obstet Gynaecol* **93**, 1262-1267.

Authors' reply

Dear Sir,

We agree with Professor Chamberlain that the data presented in our article do not prove that staff level has a causal role in circadian variation of perinatal mortality rate in Ticino. However, when considering a possible cause for the observed pattern, the striking variation of staff levels in hospital is an obvious candidate and therefore deserves attention in further studies.

Concerning the bulge of births occurring between 07·00 and 14·00 hours in Ticino, we would point out that this situation is basically similar to that observed in Switzerland (Martin-Béran & Paccaud 1986). Furthermore, the differences between the situation in Ticino in 1979–1982 and the one reported in the British

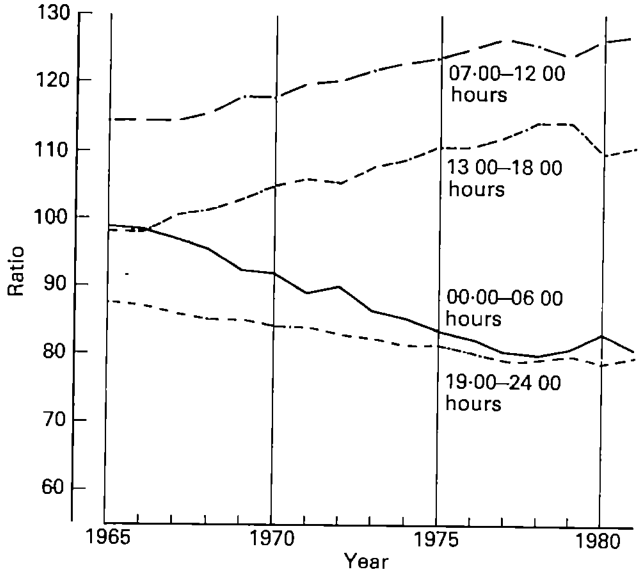

Fig. 1. Secular change in the ratio of observed to expected number of births by hour of birth in Switzerland, 1965–1981

Births 1970 study (Chamberlain *et al.* 1978) may be attributable to a secular change.

Figure 1 shows that between 1970 and 1980, the distribution of births by hour of day changed rapidly in Switzerland, with a very obvious concentration of births during the working hours (07·00–18·00 hours). A similar evolution could have occurred in Great Britain during this period and therefore account for the difference mentioned.

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Day case laparoscopic sterilization—time for a rethink?

Dear Sir,

We read with interest the article by Thomas & Hare [*Br J Obstet Gynaecol* (1987) **94,** 445–448]. In our experience, women in a 1-day surgery programme are more satisfied than is suggested by their conclusions.

We started 1-day gynaecological surgery in April 1985, and up to 1 April 1987, we had handled 639 cases of minor gynaecological surgery under general anaesthesia, of which 339 were laparoscopic sterilizations. In the same period 536 laparoscopic sterilizations were performed under local anaesthesia.

We have adopted the following procedure: women asking for sterilization are offered the choice between local or general anaesthesia; those choosing general anaesthesia are given oral and written explanations by the gynaecologist and by the nurse. We always check whether somebody can take care of the children the night after surgery and the patient receives a letter which asks her general practitioner to take charge when she returns home. Two weeks later the patient is seen by the anaesthetist; after physical examination and a check of the laboratory results, the patient is accepted or refused for the programme.

When there are are no contra-indications the patient is admitted to the day-care unit of the department of obstetrics and gynaecology 1–2 weeks later. Patients arrive at 07.00 hours. The operating list starts at 07.45 hours in the operating theatre of the hospital with the 1-day surgery cases. The patient stays for 1 h in the recovery room and is brought afterwards to the day-care unit. Between 16.00 and 17.00 hours, the patients are seen both by the gynaecologist and the anaesthetist. After complete recovery they are discharged at 18.00 hours. Drugs for pain relief are offered. Only 7 of the 339 patients had to stay overnight and were able to leave the next morning.

All the patients were seen at the out-patient clinic 4–6 weeks later when they were asked about any subsequent problems. Sixteen women said that they would have preferred a longer stay in the hospital, and 10 of them had called the general practitioner for help on the evening of the surgery although readmission was unnecessary.

Of the 339 women 297 were able to resume their normal activities 2 days after surgery and only eight said that they were not able to do their normal work after 4 days, seven of them had an umbilical haematoma.

We feel that good counselling, co-operation between gynaecologist and anaesthetist and meticulous organization of the unit are necessary when undertaking 1-day surgery and under these conditions most patients are satisfied.

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British Journal of Obstetrics and Gynaecology
September 1987, Vol. 94, pp. 926–928

BOOK REVIEWS

Future Aspects in Contraception: Part 1 Male, Part 2 Female edited by B. Runnebaum, T. Rabe & L. Kiesel. MTP Press, Lancaster, 1985, Part 1: 270 pages, Part 2: 372 pages, with figures and tables, £65.00 each

These two books consist of the Proceedings of an International Symposium on Contraception that was held in Heidelberg, West Germany in September 1984. They separately address all the major advances in contraception in the male and in the female. Their content covers a vast volume of varied and interesting research work into the wide field of contraception in both sexes.

Part 1 is, for the most part, devoted to contraception in the male but begins with an excellent and well-referenced review of the future aspects of contraception in both the male and the female. The subjects covered by the many papers published in this volume include the role of steroids, GnRH agonists and gossypol as contraceptive agents in the male. Included also is a review of the possible role of monoclonal antibodies directed against the surface antigens of sperm and their use in contraception

Part 2 is a larger book and relates to contraception in the female. It begins with chapters on all the aspects of natural family planning and also the problems and advantages of barrier contraception. Included are papers on steroid and oral contraceptives and a discussion on routes of delivery of the steroid agents. There is also a good review of postcoital contraception. A great deal of space is rightly given to the role of GnRH agonists and antagonists as contraceptives. The book also contains a series of papers on long-term clinical experiences with a variety of IUCDs, and particularly impressive was a section on the morphological changes on the surface of IUCDs by Drs Keith Bailey and Berger which is illustrated by superb scanning electron micrographs of IUCDs after long-term use. The use of the antiprogesterone agent RU486 and prostaglandins as contraceptives are discussed and there are also chapters on the use and practicalities of immunocontraception in the female. However, I was surprised to find no real attention was paid to the surgical methods of birth control either in the male or in the female.

Part 2 concludes with sections on the Politics of Contraception and the Failure of Contraception in both sexes.

These two volumes cover all the important areas of non-surgical contraception that are under study or review today and I learnt a great deal from reading them. Personally I would have preferred to have all these papers in one volume instead of two, but perhaps it was felt that male and female contraception would attract different groups of readers and that dividing the subject would help to reduce the cost of purchase.

These volumes will be of great interest to all those involved in family planning. There is also a large amount of basic information which would be of value to interested medical students. I would certainly recommend the inclusion of *Future Aspects in Contraception: Male and Female* in a medical library.

Anne Jequier

Anaesthesia for Obstetrics Second Edition edited by S. M. Shnider & Gerson Levinson. Williams & Wilkins, Baltimore, 1986, 566 pages with figures and tables, £56.00

This is a lengthy and reasonably competent addition to the increasing accumulation of books on the subject. The lengthiness is in part due to considerable repetition of accounts of the basic physiology of pregnancy (stricter editorial discipline could have overcome this), and partly reflects the fact that a significant proportion reads more like a book on medical diseases rather than one on anaesthesia, although none the worse for that. Indeed, in one chapter the only reference to anaesthetic management is the admonition that the patient should be given plenty of oxygen and not rendered hypotensive!

The quality of the chapters varies considerably. Some are outstandingly good, for example, on pre-eclampsia (although I was disappointed by the omission of reference to the condition of the spiral arteries in this disease, and its considerable relevance to anaesthetic practice); others have little relevance to UK practice (on inhalational analgesia, for example); others reflect the continuing faith held in the USA that, regarding placental vascular dynamics and other functions, conclusions drawn from animal experiments can confidently be applied to the human female; and others, frankly, are simply reprints from the previous edition. The latter has led to the inclusion of remarks such as that the perinatal mortality among infants delivered by section when <30 weeks gestation is 60–70%, to the omission of consideration of mothers with kyphoscoliosis or intracranial tumour, and of the use of salbutamol to induce myometrial relaxation. A further result is that whereas only 23% of the articles and books referred to were published after 1980, 45% appeared before 1975.

I have been rather more tart in this review than is my wont. Perhaps I was unduly provoked by the editors' statement, in their preface, that their first edition 'rapidly became the standard textbook in obstetric anaesthesia'. On my departmental shelves I have at least nine books—in the English language—devoted to the topic and published in the current decade, each of considerable merit. It should surely be left to reviewers or advertisers to project the assessment quoted. However, it is certainly a very worthy addition to the library.

J. Selwyn Crawford

Manual of Fetal Echocardiography by Lindsey D. Allan. MTP Press Ltd, Lancaster, 1986, 175 pages with figures and tables, £22.50

This book is described as a photographic instruction manual and practical guide to fetal echocardiography and there is no one better qualified to give such guidance than Dr Lindsey Allan. She starts on a rather defensive note by quoting Kipling: 'If you can trust yourself when all men doubt you . . .' which I interpreted, rightly or wrongly, as a response to those sceptics who wonder if fetal echocardiography really is of any practical value. Is there ever a case for termination of pregnancy, for example, when even the anomaly of hypoplastic left heart is no longer, with surgical advances, said to be universally fatal? Are there indeed real benefits to be obtained from planned delivery of babies with congenital heart disease close to regional cardiac surgery units? Is routine screening for cardiac malformations really helpful and cost effective, or is it merely an expensive source of unnecessary anxiety? It is disappointing that these questions are not addressed in the book but the emphasis is very firmly on practical aspects of ultrasound examination of the fetal heart. In this, the author has given an excellent account of anatomy, technique and the pitfalls of examination. A large variety of malformations are described and illustrated and the adjunctive use of Doppler ultrasound explained. The book is copiously illustrated with photographs of ultrasonograms which are generally of high quality although, in places, they are uncomfortably far removed from the relevant text. Dr Allan concludes her guide with an interesting discussion of therapeutic interventions for fetal arrythmias including the astonishing prospects of direct current cardioversion and transabdominal pacing. Those ultrasonographers whose interests in the fetal heart are less ambitious will still find this a very useful book.

J. P. Neilson

Neurological Assessment During the First Year of Life by Claudine Amiel-Tison & Albert Grenier. Oxford University Press, Oxford, 1986, 196 pages with figures and tables, £30.00

Obstetricians carrying out studies with the infant's neurological status as an end point would like to have clear data on normality or abnormality graded preferably on a numerical basis. Such has been the development of technology for investigating the neonatal brain structurally and physiologically that many paediatricians do not carry out neurological examinations on sick or small newborn infants. This book panders to neither of these tendencies. Dr Amiel-Tyson is one of the half dozen or so neurologists to have dominated the neonatal field internationally over the last 15 years, although she has not previously published extensively in the English language. These authors describe their methods for neurological examination from preterm birth to one year and the diagnosis of motor abnormalities including cerebral palsy.

The book is refreshingly personal in its writing, e.g. 'analysis of muscle tone is a field almost exclusively French' and 'neurological examination must not bore the newborn'. The techniques are as well described as is possible in a book, using words, line drawings and photographs. The appendix provides useful charts that can be used for recording neurological findings. The sequence in changes in tone and motor acquisition during the first year is very well presented. The authors argue against the use of single numerical scores to encapsulate neurodevelopmental status.

One might disagree on specific points. For example no distinction is made between the performance of a full term neonate in the first week and a 3-month-old baby who was born at 28 weeks gestation. Many neurologists find significant differences between such infants who are at the same postmenstrual age.

The translation from the original French to English lapses only very occasionally. I was mystified by the word 'impotence' which I think should be 'importance' and 'semiology' does not appear in my two-volume Oxford English Dictionary. On the other hand there are some valuable new concepts such as 'liberated motor activity' and 'state of communication' which one does not find in other books on neonatal neurology.

Obstetricians requiring their paediatric colleagues to make thorough neurological assessments on the infants they deliver should make sure that they have this volume.

A. G. L. Whitelaw

Books received some of which may be reviewed at a later date

Ovarian Malignancies: Diagnostic and Therapeutic Advances (Clinical Obstetrics and Gynaecology) edited by M. Steven Piver. Churchill Livingstone, Edinburgh, 1987, 302 pages with figures and tables, £45.00

Progress in Obstetrics and Gynaecology Volume 6 edited by John Studd. Churchill Livingstone, Edinburgh, 1987, 442 pages with figures and tables, £19.95

Reproductive Physiology in Clinical Practice edited by Daniel H. Riddick. Thieme Medical Publishers, Inc., New York, 1987, 277 pages with figures and tables, DM 168

Postgraduate Medical Education and Training: The System in England and Wales by Robin Dowie. King Edward's Hospital Fund for London, Oxford University Press, 1987, 357 pages with figures and tables, £35.00

Neonatology: A Practical Guide Third Edition by Alistair G. S. Philip. W. B. Saunders Co., London, Philadelphia, 1987, 559 pages with figures and tables, £14.95

The Psychology of Childbirth by Joyce Prince & Margaret E. Adams. Churchill Livingstone, Edinburgh, 1987, 219 pages, illustrated, £7.95

Baillière's Clinical Obstetrics and Gynaecology Volume 1, Number 1. Fetal Monitoring. March 1987 edited by Martin John Whittle. Baillière Tindall, London, Philadelphia, 222 pages with figures and tables, £15.00 (UK and Eire), $25.00 (USA and Canada), £18.00 (all other areas)

1987 Year Book of Obstetrics and Gynecology edited by Daniel R. Mishell Jr, Thomas H. Kirschbaum & C. Paul Morrow. Year Book Medical Publishers, Inc., Chicago, London, 1987, 592 pages with figures and tables, £36.50

Advances in International Maternal and Child Health Volume 7 edited by D. B. Jelliffe & E. F. Patrice Jelliffe. Oxford University Press, Oxford, 1987, 201 pages with figures and tables, £25.00

Neonatology. A Practical Guide Third Edition by G. M. Gandy & N. R. C. Roberton. Blackwell Scientific Publications, Oxford, 1987, 363 pages with figures and tables, £8.95

Your Smear Test: A Guide to Screening, Colposcopy and the Prevention of Cervical Cancer by Graham H. Barker. Adamson Books, London, 1987, 128 pages, illustrated, £4.95

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Trudinger, B J , Lewis, P J & Petit, B (1979) Fetal breathing in intrauterine growth retardation *Br J Obstet Gynaecol* **86**, 432-436

Hytten, F E & Leitch, I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p 26

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British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten

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Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications
BJOGAS 94(10) 929–1008 1987 ISSN 0306-5456

British Journal of Obstetrics and Gynaecology

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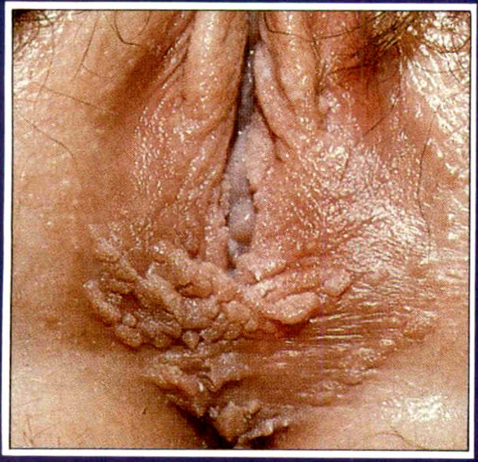

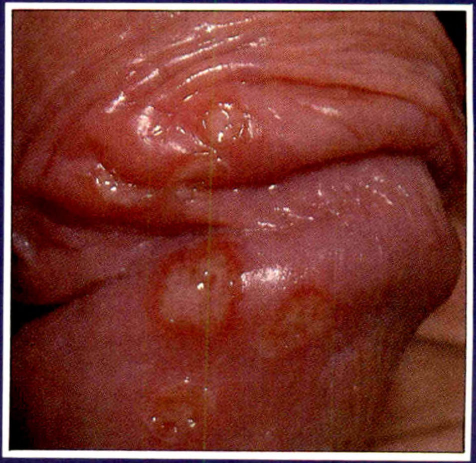

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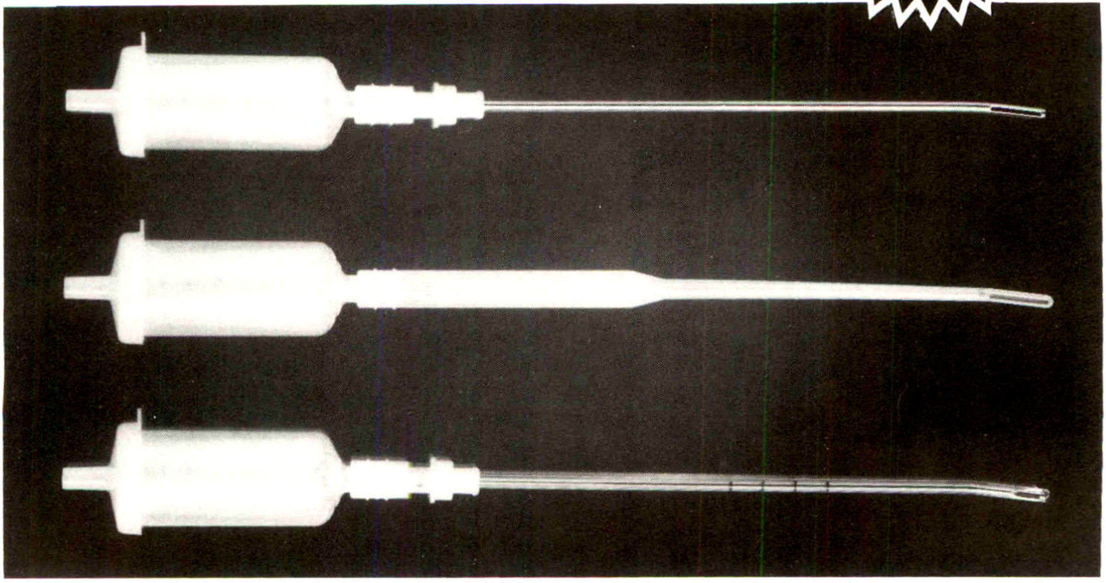

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Technical Data Overleaf

TECHNICAL DATA

DATA SHEET

PDS* (Polydioxanone) Sterilised Monofilament Synthetic Absorbable Suture

Presentation

PDS (Polydioxanone) Monofilament Synthetic Absorbable Suture is prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding either D & C blue No 6 (gauges metric 0.2 and 0.3, 10/0 and 9/0) or D & C violet No 2 (gauges metric 0.4 to 5.0 8/0 to 2) during polymerisation. These sutures may also be manufactured undyed (clear).

PDS (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action

Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Data obtained from implantation studies in rats show that, at two weeks post implantation, approximately 70% of the suture strength is retained whilst at four weeks the strength retention is approximately 50%. At eight weeks approximately 14% of the original strength remains. *This indicates a significantly longer period of wound support than previously available with an absorbable suture*

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within six months.

Uses

PDS (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration

By implantation.

Contra-indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal epithelium sutures could cause localised irritation if left in place for longer than 10 days. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

The safety and effectiveness of PDS (Polydioxanone) sutures in neural and cardiac tissue have not been established.

Pharmaceutical Precautions

Do not re-sterilise.

Legal Category P

Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities

The gauge range initially available will be 0.2 metric (10/0) to 5 metric (2). Various lengths of material attached to non traumatic stainless steel needles are packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sale is 12 or 24 packs contained in a film wrapped drawer style carton.

Further Information

No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos 0508/0011 (dyed); 0508/0012 (clean.
Br Pat No 1 540 053.

Date of preparation of Data Sheet – September 1982
Revised 8/1986

DATA SHEET

Coated VICRYL* (Polyglactin 910) Sterilised Braided Synthetic Absorbable Suture

Presentation

The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action

Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses

Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration

By implantation

Contra-indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days and should be removed as indicated.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when coated VICRYL sutures are used in ophthalmic procedures.

The safety and effectiveness of Coated VICRYL (polyglactin 910) Sutures in neural tissue and in cardiovascular tissue have not been established.

Pharmaceutical Precautions

Do not re-sterilise.

Legal Category

Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities

Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

Further Information

No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence No 0508/0009
Br. Pat. No. 1583390

Date of Preparation of Data Sheet April 1981
Revised 4/1987

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Full prescribing information including product Data Sheet is available from:

Serono Laboratories (UK) Ltd., 2 Tewin Court, Welwyn Garden City, Hertfordshire AL7 1AU. Telephone: Welwyn Garden (0707) 331972

References

1 Franks, S. et al. – J. Endocrinol. (1985) 104 p. 34. Abst. 41
2 Yen, S.S.C. et al. J. Clin Endocrinol. Metab. (1970) 30. pp 435-442
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5 Braendle, W. et al. "Advances in Diagnosis and Treatment of Infertility" Ed. V. Insler and G. Bettendorf (1981) pp 33-41, Elsevier, North Holland
6 Gocial, B. Wu, C.H. et al. Society for Gynaecological Examination 31st Annual Meeting, San Francisco (21-24 March 1984) Abstract No. 279, pp 164

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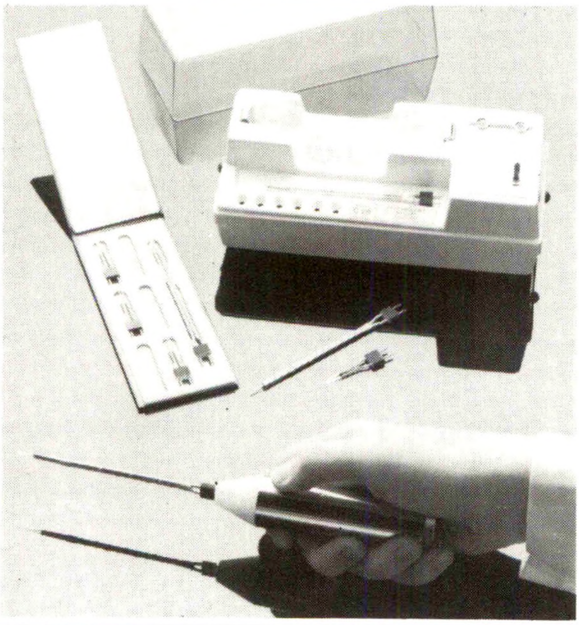

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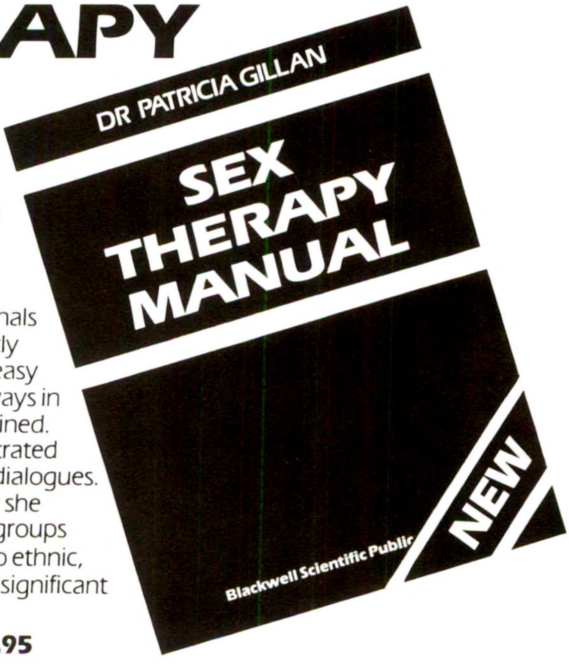

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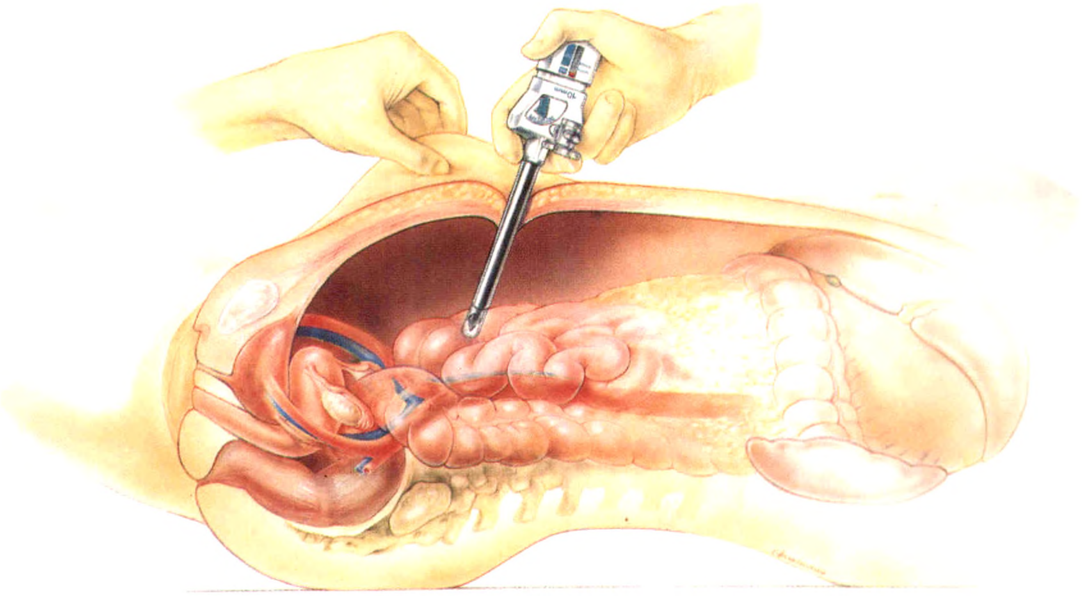

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1. Sato, T., Ibuki, Y., Hirono, M., Igarashi, M. and Matsumoto, S. (1969) Fert. Steril. **20:** 965. 2. Persson, B.H. (1965) Acta. Soc. Med. Upsala **70:** 71. 3. Berger, M. (1972) Schweiz Z. Gynak. Geburtsch **3:** 209. 4. Mellega, C., Hasonni, V.M., di Leo, A., Venturoli, S., Fuschini, G. and Flamigni, C. (1977) Acta. Europ. Fert. **8:** 119.

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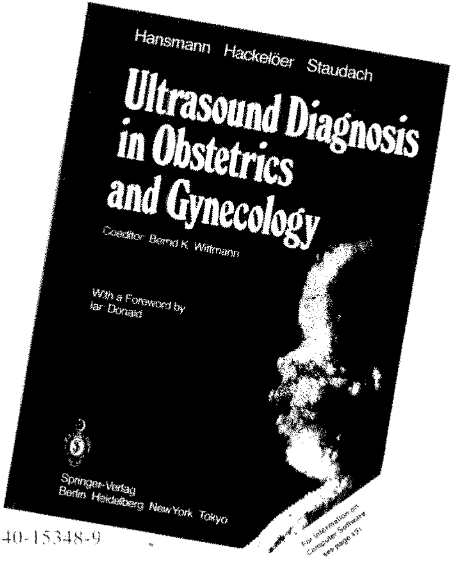
Translated from the German by T.C. Telger
Coeditor of the English edition: **B. K. Wittmann,** Vancouver
With a Foreword by **I. Donald,** Glasgow

1986. 589 figures. XVIII, 495 pages. Hard cover DM 280,–. ISBN 3-540-15348-9
German edition also available



Hansmann Hackelöer Staudach
Ultrasound Diagnosis in Obstetrics and Gynecology
Coeditor Bernd K. Wittmann
With a Foreword by Ian Donald
Springer-Verlag
Berlin Heidelberg New York Tokyo

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Contents: Physics and Instrumentation in Diagnostic Ultrasound. – Safety of Diagnostic Ultrasound. – Examination of the Female Pelvis. – Pregnancy (First Trimester). – Multiple Pregnancy. – Amniocentesis. – Normal Fetal Anatomy in the Second and Third Trimester. – Fetal Malformations. – Rhesus Incompatibility and Nonimmunologic Hydrops Fetalis. – Phenotype and Rare Syndromes. – The Placenta. – The Cervix. – Postpartum Ultrasound. – Ultrasound Screening. – Sonographic Aspects of the Menstrual Cycle. – Pathology of the Genital Tract. – Intrauterine Contaceptive Devices. – Diagnosis of Breast Disease. – Appendix. – Subject Index. – A Simple Reporting Program for Obstetrical Ultrasound.

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British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp 929–934

COMMENTARY

Doppler ultrasound

Doppler ultrasound has been used for several years to study the pattern of blood flow in vessels in adults. Its more recent application to obstetrics is now the focus of much interest and research activity. The more optimistic view is that, in Doppler ultrasound, we have at last a safe, non-invasive, repeatable and reliable technique to assess maternal blood flow to the placenta: further, because the cardiovascular responses of the fetus may also be studied, a definitive method of investigating uteroplacental insufficiency may have been achieved. The more pessimistic view is that here, yet again, we see a technique of unproven value, based on uncertain principles, being introduced prematurely into clinical obstetric practice. This is a suitable time for a dispassionate review of the subject.

Two different types of Doppler equipment may be used: continuous wave systems which are relatively inexpensive and simple, and pulsed wave systems which have the advantage of allowing the blood vessel to be imaged and range gating performed. Some of the latter systems (at least those used for peripheral vascular work) may use energy outputs in excess of the recommended maximum in pregnancy (Preston 1986) and research workers (and hospital ethics committees) should be aware of the characteristics of their individual systems. The quantitation of blood flow is difficult because this necessitates accurate knowledge of various elements, including vessel diameter, which are not readily obtained. Most workers, instead, now use some method of waveform analysis which compares the velocities of blood during systole to those at the end of diastole.

Vessels on both sides of the placenta have been studied starting with the work of Fitzgerald & Drumm (1977) on the umbilical artery and now include the umbilical vein, the fetal aorta and internal carotid artery, and branches of the maternal uterine artery; the umbilical artery remains the most popular vessel for study. Both the uteroplacental and fetoplacental circulations are usually low resistance systems in which downstream flow continues throughout the cardiac cycle. When vascular resistance increases, diastolic flow may decrease, stop or even become reversed and this is reflected in the blood velocity waveform.

Failure of the physiological invasion of myometrial spiral arteries by cytotrophoblast early in the second trimester (Khong *et al.* 1986) and the later development of acute atherosis would both be expected to be associated with higher vascular resistance; both phenomena may be associated with pre-eclampsia and with fetal growth retardation. Thus, in theory, diminished diastolic blood flow velocities in the uterine arterial system may not only identify uteroplacental insufficiency but might also give early warning of it long before the clinical features become obvious.

The impact of uteroplacental insufficiency on fetal umbilical artery waveforms is less easily predicted. However, in a small study of pregnant sheep, embolization of the uterine circulation with microspheres produced a rapid increase in umbilical artery resistance if fetal growth retardation were to result later (Clapp *et al.* 1980). Although direct extrapolation of these findings to human pregnancy must be avoided (Mellor 1984), a similar phenomenon is recognized in the human fetus and has been ascribed to vascular abnormalities in tertiary stem villi (Giles *et al.* 1985*a*) or to increased fetal blood viscosity (Erskine & Ritchie 1985) although the nature of the pathophysiology remains uncertain. This gap in understanding would be of less importance if clinical studies were to show the technique to be helpful. The clinical areas in which Doppler would be most likely to be of value are in identifying or predicting fetal growth retardation, determining pathophysiology when a fetus is identified as small-for-dates, assessing fetal well-being and assessing twin pregnancies. It may also prove to have a role in investigating vasoactive drugs during pregnancy (Rubin 1987).

Much of the work published to date has concentrated on predicting babies that are small-for-dates at birth. Comparison between reports is difficult because of varying diagnostic criteria, selection of patients and vessels studied but a comprehensive review of available data (Neilson & Whittle 1987) suggests that fetal measurements with diagnostic ultrasound give better prediction. This is not at all surprising in view of the heterogeneous nature of the small-for-dates group, but it emphasizes the importance for researchers to investigate alternative and better indices of fetal growth retardation. The much advertised claim that Doppler study of the 'arcuate' artery at around 18 weeks is a useful screening technique for predicting subsequent uteroplacental insufficiency (Campbell *et al.* 1986) does not stand up to critical analysis of the available data. A screening test which shows no less than 40% of unselected (and therefore presumably normal) pregnancies to have results more than two standard deviations above the mean either holds little promise or requires further study.

Whether it is possible, using Doppler, to separate anatomically normal small-for-dates fetuses into growth retarded and non-growth retarded subgroups, would seem a more fruitful area of investigation, the hypothesis being that those that are genuinely growth retarded would be associated with abnormal flow variables on the maternal side of the placenta. Studies which have addressed this question (Campbell *et al.* 1983; Trudinger *et al.* 1985) have been difficult to interpret because of differing mean gestational age in the two subgroups.

It seems possible that the main contribution of Doppler flow studies will be in predicting adverse outcome, thus aiding the planning of delivery. A total of nine intrauterine deaths reported in pregnancies with abnormal umbilical artery waveforms have been reviewed (Neilson & Whittle 1987). In some cases major fetal compromise was already evident and knowledge of Doppler flow studies would have made little or no difference to management or outcome. Of particular interest, however, is the intrauterine death associated with abnormal waveforms reported by Schulman *et al.* (1984) which occurred in an apparently normal pregnancy studied solely for research purposes. Whether such unexpected and unexplained deaths can be predicted, by routine screening of all patients, merits further investigation. On the debit side, Erskine *et al.* (1986*a*) report an unexplained intrauterine death occurring within 12 h of normal Doppler studies (and non-stress cardiotocography). Comparison with alternative methods of fetal assessment requires further research and, while it has been suggested that velocity waveform changes precede abnormal cardiotocography (Trudinger *et al.* 1986), these may not clearly indicate the optimal time at which intervention is advisable.

Doppler ultrasound may also have a role to play in assessment of multiple pregnancies both in identifying growth retardation which is common and also the twin-to-twin transfusion syndrome which is not. Reports of umbilical artery waveforms in twin-to-twin transfusion have described concordant (Giles *et al.* 1985*b*), discordant (Farmakides *et al.* 1985) and variable (Erskine *et al.* 1986*b*) patterns and there may be no consistent picture.

I have concentrated on studies of the umbilical artery but, as was mentioned, other vessels have also been investigated and, indeed, the study of different vessels in the same fetus may identify differential cardiovascular responses to hypoxia. Thus Soothill *et al.* (1986) described a strong negative correlation of fetal hypoxia (as diagnosed by analysis of fetal blood obtained by needling the umbilical vein) with mean velocity of blood in the fetal aorta (as assessed by Doppler ultrasound). Wladimiroff *et al.* (1986) studied a series of small-for-dates fetuses with Doppler equipment and reported increased vascular impedance in the aorta together with decreased impedance in the internal carotid artery. These findings are compatible with the well recognized, compensatory 'brain sparing' effect found when hypoxia is induced in experimental animals.

It has been suggested by Hackett *et al.* (1987) that differential alterations in regional blood flow may result in tissue ischaemia to produce such neonatal complications as necrotizing enterocolitis. They found that of 26 small-for-dates babies, which as fetuses had absent end-diastolic aortic blood flow, seven developed necrotizing enterocolitis after delivery. However, six of these babies not only weighed less than 1 kg at birth but also had coexisting respiratory distress and it may well have been that the Doppler investigations were of less prognostic value than the dire clinical backgrounds. It is to be hoped that this interesting finding will be investigated further by prospective study. The King's College Hospital Group have more recently reported prolonged maternal oxygen therapy in five pregnancies complicated by fetal growth retardation during the second trimester (Nicolaides *et al.* 1987). In each case the mean blood velocity in the fetal aorta appeared to increase in response to this therapy but regrettably the study was uncontrolled and therefore is of limited interest.

A dispassionate view of Doppler ultrasound, at present, indicates a need for much more work before any consideration of clinical application. There is a need to understand the pathophysiology of abnormal waveforms, to establish the optimal vessel or vessels for study and the optimal form of waveform analysis, to establish suitable endpoints for clinical studies in broadly based groups and, finally, to assess the impact on fetal outcome and pregnancy management by randomized controlled trials. Trudinger *et al.* (1987) have recently reported a controlled trial of 300 hospitalized antepartum patients who underwent umbilical artery Doppler study with the results of 133 reported and those of the other 167 concealed. There was a lower incidence of caesarean section during labour in the reported group although overall caesarean section rates (and other indices of outcome) were not significantly different between the groups. The Sydney team are to be congratulated on mounting a controlled trial at this time but the question of whether Doppler ultrasound actually improves management or outcome remains open.

There is nothing in the published literature to indicate that the impact of Doppler ultrasound will be of such overwhelming value that it should be rushed into clinical practice without proper assessment. Until it is properly assessed, its clinical use should be deprecated as should extravagant claims based on inadequate data.

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Renal biopsy during pregnancy: 'To b . . . or not to b . . .?'

Safety of, as well as indications for, performing percutaneous renal biopsies during pregnancy are currently unclear. In this issue (pp. 935–939) Packham & Fairley describe their own experience and concluding that there is no increase in risk, they suggest that closed biopsies ought to be performed more often in pregnant women. This, they claim, is because certain glomerular disorders are adversely affected by pregnancy, and that the gestationally induced progression of these diseases might be blunted by specific therapy such as antiplatelet agents. A review of the debates that have surrounded these issues is in order.

Introduction of closed renal biopsy techniques in the 1950s revolutionized our understanding of kidney pathology as well as the natural history of many specific disorders. It was only a matter of time before the procedure was extended to pregnancy with similar progress, primarily in the area of pre-eclampsia. Renal biopsies were performed for the same diagnostic indications used for non-pregnant subjects, but the primary use of this procedure in pregnant women was to differentiate the various causes of hypertension during the latter half of pregnancy. At that time it was believed that demonstrating the characteristic lesion of pre-eclampsia would be an indication to terminate the pregnancy, while observation of another lesion might lead to specific therapeutic interventions which might ensure continuation of the pregnancy to a point where fetal survival would be improved. Here is where most of the trouble apparently began.

Schewitz *et al.* (1965) published an oft quoted report entitled *Bleeding after renal biopsy in pregnancy*. This group had initially (from 1954–1959) noted few adverse reactions and had considered the procedure safe, but in their next 77 biopsy attempts 16·7% of the women experienced gross haematuria, 4·4% perirenal haematomas and there was one maternal death, a very worrying statistic indeed. In 1975 and again in 1977 one of us (M.D.L.) analysed the experience at his own institution (Lindheimer *et al.* 1975, Lindheimer & Katz 1977), reviewed the literature and concluded as follows. In series where major complications were increased, many of the biopsies had been performed antepartum and in some tissue was obtained via the peritoneal route during caesarean section. Women had frequently been biopsied while still hypertensive, and much of this experience predated recognition of the coagulation abnormalities which may accompany pre-eclampsia. At Chicago Lying-In Hospital, McCartney (1964) had observed gross haematuria in only 3·5% of 400 renal biopsies from pregnant and puerperal patients. Transfusion had been required in three (two of whom had undergone the procedure during caesarean section) and one patient had required nephrectomy. Other experiences from most other centres (cited by Lindheimer *et al.* 1975 and Lindheimer & Katz 1977) were similar to those of McCartney (1964): that is complications after renal biopsies appeared no different from those in non-pregnant patients. Our own observations then included 60 biopsies performed in the immediate puerperium in which no instances of gross haematuria had occurred, but one woman, who it turned out had severe disease involvement of the renal vasculature, had a perirenal haematoma and required transfusions.

Packham & Fairley report on 111 renal biopsies in 104 pregnant women, all performed before 29 weeks gestation, confirming and extending the previous contention that risks of the procedure resemble those in the non-pregnant population. In fact their incidence of transient gross haematuria, 0·9% (all patients undergoing biopsy have *microscopic* haematuria unless one has missed the kidney!), is considerably lower than the experience in non-pregnant patients where the incidence is 3–5% These excellent statistics relate in part to Dr Fairley's technical skills and his 20 years of experience with the procedure. Statistics are probably also improved by refinement over the years of pre-biopsy assessment which includes ensuring that the patient has not ingested drugs which interfere with clotting (i.e. aspirin) for at least 7–10 days before the procedure, as well as the usual tests to exclude bleeding diatheses.

Now that there is a consensus that pregnancy adds little or no risk to the procedure and given the fact that complications do occur, what are the indications to perform a kidney biopsy in a pregnant woman? Here we disagree with the broad indications cited by Packham & Fairley, and conclude that it should be done 'very infrequently'. Even in non-pregnant populations reasons for renal biopsy, while 'broad', are not clearly defined and experts categorize indications with terms such as 'most useful', 'possibly useful' and of 'little or no use' (Cutler & Striker 1983). The following summarizes our current 'indications' which have been revised from those suggested 10 years ago (Lindheimer *et al.* 1975; Lindheimer & Katz 1977)

We recommend biopsy when there is sudden deterioration in renal function before 32 weeks gestation and no obvious cause is apparent. This is because certain forms of rapidly progressive glomerulonephritis may respond to aggressive treatment with steroid 'pulses', chemotherapy and perhaps plasma exchange when a diagnosis is made at an early stage. Moreover, precise knowledge of the lesion associated with acute renal failure may alter therapy. For instance, observations of interstitial nephritis would lead to reassessment of the patient's medications, and we are aware of one rare instance where non-caseating granulomas were identified and the pregnant woman, then undergoing dialysis, responded to steroids with a return of renal function and successfully completed the pregnancy Parenthetically the kidney was the only organ involved in this patient with sarcoidosis (G. V Warren *et al.*, personal communication).

Another situation in which biopsy is recommended is when there is *symptomatic* nephrotic syndrome before 32 weeks gestation. Some might consider a test of steroids alone, but since pregnancy is already a hypercoagulable state we prefer to identify the lesions which might respond before initiating steroid treatment. We wish to emphasize that presence of proteinuria alone in a normotensive woman with well preserved renal function, who has neither marked hypoalbuminaemia nor intolerable oedema would lead us to examine the patient at more frequent intervals but biopsy would not be performed during gestation This is because in our experience (Katz *et al.* 1980) confirmed by others (Surian *et al* 1984; Abe *et al.* 1985; Jungers *et al.* 1986; Barcelo *et al.* 1986), it is primarily the level of renal function and the absence or presence of hypertension which are of prognostic importance. We take a similar position in the management of pregnancies with asymptomatic microscopic haematuria alone when neither stone nor tumour are suggested by ultrasonography. Moderate or severe hypertension of any cause is treated similarly, failure to control the blood pressure being one reason to suggest termination. Here too, performance of a renal biopsy adds little or nothing to the final clinical decision.

One grey area is a presentation characterized by an active urinary sediment (red and white blood cells and casts) with proteinuria and borderline renal function, in a patient who had not been previously assessed. One could argue that diagnosis of a collagen disorder such as scleroderma or periarteritis would be grounds for termination of the pregnancy or that classification of the type of lesion in a woman with lupus erythematosus would determine the extent of the therapeutic regimen. The first two diseases are rarely diagnosed by renal biopsy and a normotensive woman with stable renal function and neither systemic nor laboratory evidence of any of these collagen disorders, is watched closely without intervening.

In summary, pregnancy does not increase the risks of renal biopsy. There are indications for its use such as sudden renal failure or massive nephrotic syndrome of unknown origin, occurring before the final 2 months of pregnancy. Such occurrences are fortunately unusual. On the other hand, the antenatal progress of women with mild or moderate proteinuria and/or asymptomatic microscopic haematuria who are normotensive and have well preserved renal function should be monitored frequently and a more extensive assessment of their disease deferred to the postpartum period.

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British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp 935–939

Renal biopsy: indications and complications in pregnancy

DAVID PACKHAM, KENNETH F. FAIRLEY

Summary. A series of 111 renal biopsies performed in 104 pregnant women during the past 20 years at The Royal Melbourne Hospital and Royal Women's Hospital, Melbourne were reviewed. The indications for biopsy and the histological findings are detailed. The complication rate was very low (4·5%). It is concluded that the procedure is safe and that renal biopsy during pregnancy yields a definitive histological diagnosis in almost all cases. The indications for renal biopsy in pregnancy are discussed.

Renal biopsy of patients presenting during pregnancy with signs of renal disease is normally deferred until the postpartum period. This deferral is, in part, due to a report of increased risk of closed biopsy 20 years ago and, in part, because the histological changes of glomerular disease may be obscured by changes resulting from the pregnancy itself.

We report a consecutive series of 111 renal biopsies performed on 104 pregnant women during the past 20 years at the Royal Melbourne Hospital and Royal Women's Hospital, Melbourne.

Patients and methods

The findings in a consecutive series of 104 pregnant women admitted for renal biopsy between 1965 and 1985 were reviewed. The age, parity and gestation of the women were recorded. The identity of the physician performing the biopsy, the imaging technique employed and the type of biopsy needle used were also noted. Before the biopsy all women had a normal platelet count, bleeding time and clotting profile. The majority of the biopsies (90) were performed by the same physician (K.F.). In 101 biopsies very brief fluoroscopic screening, with shielding of the fetus, was used to establish the site of the lateral renal margin and to exclude abnormalities of renal anatomy. The remaining 10 biopsies were performed under ultrasound guidance In 101 biopsies a Franklin modification of the Vim Silverman needle, and in 10 a Trucut biopsy needle, was used. All biopsies were performed in the prone position. After the procedure the patients remained in bed for 24 h and were normally discharged 24–48 h after the biopsy. During this period blood pressure, any bleeding from the biopsy site, loin pain, macroscopic and microscopic haematuria were recorded. Renal biopsies were processed as described elsewhere (Kincaid-Smith *et al.* 1985).

We have defined glomerular haematuria as >8000 rbc/ml; proteinuria in pregnancy as >0·3 g/24 h; nephrotic range proteinuria as >5 g/24 h, arterial hypertension as a diastolic pressure >90 mmHg or requiring anti-hypertensive therapy; and impaired renal function as creatinine clearance <1·5 ml/min or a serum creatinine >0·10 mmol during pregnancy. The presence of these indications at the time of biopsy was noted. It should be noted that in every case the indications quoted for biopsy were observed during the first or second trimes-

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Table 1. Indications cited for renal biopsy in 76 patients presenting for the first time in pregnancy

Indications	Previous obstetric history of pre-eclampsia: No (primi- and multigravidae)	Previous obstetric history of pre-eclampsia: Yes (multigravidae)
Impaired renal function	3 (4%)	3 (4%)
Nephrotic syndrome	6 (8%)	3 (4%)
Haematuria, proteinuria and hypertension	3 (4%)	5 (6·5%)
Haematuria and hypertension	0	4 (5%)
Haematuria and proteinuria	8 (10%)	20 (26%)
Haematuria	4 (5%)	2 (2·5%)
Proteinuria and hypertension	4 (5%)	2 (2·5%)
Proteinuria	1 (1·5%)	4 (5%)
Normal urinary sediment, normotensive	— —	4 (5%)
Total	29 (38%)	47 (62%)

ter of pregnancy. The previous obstetric history of multigravidas was also recorded.

Results

Overall 104 women had a total of 111 biopsies, 4 women had 2 biopsies during the same pregnancy and 3 a single biopsy in sequential pregnancies. The women biopsied were aged between 17 and 39 (median 25) years. Gestation at the time of biopsy varied between 4 and 28 weeks (median 15 weeks).

Of the 104 women, 22 had a pre-existing diagnosis of glomerulonephritis, and renal biopsy was performed in these patients to assess progression of disease during pregnancy; four of them had systemic lupus erythematosus with renal involvement. Of the remaining 82 women presenting for the first time in pregnancy, 76 had the indications for renal biopsy adequately recorded in their hospital inpatient notes (Table 1). The yield of positive histological evidence of glomerulonephritis in biopsies performed for different indications is represented in Table 2. Four patients with neither urinary abnormality nor hypertension in the index pregnancy had a history of severe early pre-eclampsia and fetal death in a previous pregnancy. In each case histological examination revealed changes of previous pre-eclampsia, but no underlying glomerulonephritis. As Table 2 shows, if these patients and those patients with isolated microscopic haematuria in the index pregnancy are excluded from analysis, then a positive histological diagnosis of glomerulonephritis was made in almost all cases (92%).

Table 3 analyses the underlying glomerulonephritis diagnosed in the 61 patients who had glomerulonephritis diagnosed for the first time in pregnancy against the indications for biopsy. Seven of nine patients presenting with the nephrotic syndrome had membranous glomerulonephritis and four of six with impaired renal function had underlying focal and segmental hyalinosis and sclerosis

Table 4 shows the complications occurring in this series of 111 biopsies. In only one woman was there a potentially serious complication, she presented at 8 weeks gestation with severe nephrotic syndrome (30 g/24 h proteinuria) shown on renal biopsy to be due to an active focal and segmental hyalinosis and sclerosis lesion. Her nephrotic syndrome failed to respond to steroid therapy and she was treated by plasma exchange. Proteinuria continued and renal function deteriorated. By 25 weeks the nephrotic syndrome and renal function were

Table 2. Relation between the indications for renal biopsy cited and a positive histological diagnosis of glomerulonephritis in 76 patients biopsied for the first time in pregnancy

Indications	Diagnosis of glomerulonephritis made on biopsy: Positive	Negative	% Positive
Previous severe pre-eclampsia but no urine abnormality nor hypertension in index pregnancy	0	4	0
Haematuria alone	0	6	0
All other indications*	61	5	92%
Total	61	15	80%

* Listed in Table 1.

Table 3. Relation between indications for biopsy and histological category of glomerulonephritis diagnosed in 61 patients with glomerulonephritis diagnosed for the first time during pregnancy

		Indication		
Diagnosis	No. (%) of patients	Impaired renal function	Nephrotic syndrome	All other indications
Mesangioproliferative (non-IgA)	12 (20)	—	—	12
IgA nephropathy	20 (33)	—	1	19
Membranous	12 (20)	—	7	5
Focal segmental hyalinosis and sclerosis	10 (17)	4	1	5
Mesangiocapillary	5 (8)	1	—	4
Focal and segmental proliferative	2 (3)	1	—	1
Total	61 (100)	6	9	46

much worse and termination of pregnancy was advised. She was reluctant to accept this advice and a renal biopsy was performed as an additional guide to mangement. Immediately after the biopsy the patient complained of loin pain and tenderness which persisted for 3 days, although no mass could be felt and there was no macroscopic haematuria. On the fourth day the patient had an antepartum haemorrhage. A premature infant was born vaginally but died within 48 h. The patient's haematocrit fell at this time and she required a 7 unit blood transfusion. Both the antepartum haemorrhage and a probable perirenal haematoma following biopsy were thought to contribute to the fall in haemoglobin. Because she was being treated by plasma exchange, this was recognized as a 'high-risk' biopsy.

One patient biopsied at 10 weeks gestation developed macroscopic haematuria which resolved within 48 h. Her haemoglobin did not fall and she did not require transfusion.

Three other patients complained of loin pain following renal biopsy. In none was there any sign of haemorrhage and pain settled with simple analgesics.

In three cases initial biopsy failed to provide sufficient renal tissue for diagnostic purposes, but in all cases a subsequent successful biopsy was performed without complications.

Table 4. Complications of renal biopsies

Complications	Number (%)
Clinical perirenal haematoma	1 (0·9)
Macroscopic haematuria	1 (0·9)
Loin pain	3 (2·7)
Failure to obtain sufficient tissue	3 (2·7)
No complications	103 (92·8)
Total	111 (100)

Discussion

The complication rate of this series of 111 consecutive renal biopsies compares very favourably with reports of large series of biopsies performed in non-pregnant subjects (Kark *et al.* 1958; Diaz-Buxo & Donadio 1975; Wikre & Gulper 1982), as does our tissue procurement rate (Bolton & Vaughan 1977). Smythe *et al.* (1964) reported a low rate of complications following renal biopsy in patients with pre-eclampsia, although their series included both patients who were pregnant and those who were biopsied in the early postpartum period.

By contrast, Schewitz *et al.* (1965) reported a much higher complication rate in pregnant women than in non-pregnant subjects who were biopsied on their unit Many of their patients were biopsied in the upright position and, in many of those who developed complications, renal medulla was obtained. Our own patients, all of whom were biopsied before 29 weeks gestation, were able to lie prone and the biopsy was performed in that position Our practice with patients presenting in the third trimester of pregnancy is to defer renal biopsy until after delivery.

The method of localization relates to our very extensive biopsy experience in this department. We perform 700–800 biopsies a year and for most of them we use fluoroscopic localization.

We do not regard ultrasound as a satisfactory method for localization. We have had a significantly higher rate of serious complications including some nephrectomies in non-pregnant patients who have had biopsies with ultrasound localization. This seems to relate to the inability to localize accurately the lateral border of the kidney. We aim to biopsy cortex only and as the cortex is only 6 mm deep accurate localization is necessary. A single short fluoroscopy in later pregnancy is very unlikely to have associated hazards and in early pregnancy the uterus is carefully screened Only the renal area is subjected to fluoroscopy.

The diagnostic value of renal biopsy performed during pregnancy on this unit is high. In 80% of patients biopsied for the first time in pregnancy a definite diagnosis of a histological type of glomerulonephritis was possible. Analysis of the indications for biopsy cited suggests that this figure might be improved still further if certain categories of indications were excluded (Table 2).

Lupus nephritis was rare in our series with only 4 of the 104 patients having this condition. In this unit, at least, it is rare for women to present during pregnancy with lupus nephritis, although we have had one such case recently (not included in this series). It is almost certain that our attitude about lupus nephritis is reflected in the paucity of cases biopsied during pregnancy. When we make a diagnosis of lupus nephritis, which we most commonly do in teenage girls, we treat the lesion very aggressively in the first instance. Pregnancy is only undertaken when biopsy returns to normal or near normal, which may be 10 years or more after presentation. In such patients there is, of course, no indication for biopsy during pregnancy.

Having established the safety and diagnostic yield of renal biopsy in pregnancy on this unit, what are the indications for its performance? Because of our evidence that certain forms of glomerular disease have more serious consequences during pregnancy, as well as after pregnancy, than others (Kincaid-Smith 1983; Becker *et al.* 1986), and particularly in view of the increasing evidence that anti-platelet drugs benefit such patients (Kincaid-Smith 1984), we are tending increasingly to make a biopsy diagnosis during pregnancy, especially as, in our hands, there is no increased risk associated with biopsy at this time. However, the effect of pregnancy on the clinical and histological course of glomerulonephritis is controversial (Fairley *et al.* 1973; Katz *et al.* 1981; Rovati *et al.* 1984; Kincaid-Smith *et al.* 1980).

Despite this, there is no doubt that different histological types of glomerulonephritis have an entirely different prognosis regardless of the impact of pregnancy (Cameron & Hicks 1984) In addition, renal biopsy early in pregnancy provides baseline histology for comparison should deterioration in renal function occur later in pregnancy Both these considerations are of importance in assisting the patient, and her physician, in a decision to proceed with her pregnancy.

In conclusion, we find that renal biopsy during the first two trimesters of pregnancy does not appear to be associated with an increased rate of complications. In addition, provided adequate clinical conditions are present, the procedure enables a classification of underlying renal disease to be made in a majority of patients.

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Received 17 September 1986
Accepted 21 April 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp. 940–948

Ultrasound measurement of fetal blood flow in predicting fetal outcome

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Summary. The efficacy of fetal blood flow assessment in predicting fetal outcome was evaluated in 159 pregnancies suspected of intrauterine growth retardation (IUGR). Blood flow in the fetal aorta and umbilical vein was measured with imaging and pulsed Doppler ultrasound. Volume blood flow values and variables describing the waveform of the maximum aortic blood velocity were checked for relations to subsequent fetal outcome A new semi-quantitative velocity waveform variable, blood flow class (BFC), was designed and tested. The occurrence of IUGR, imminent fetal distress, a low Apgar score at 1 and 5 min, and a low pH in the umbilical artery and vein were adopted to characterize fetal outcome. Receiver operating characteristic curves were used to demonstrate the sensitivity and false positive rate, and the Cohen's Kappa index was used to compare the predictive capacity of the various blood flow variables. BFC, describing the blood velocity waveform with emphasis on its end-diastolic part, was found to be the most powerful marker of imminent fetal asphyxia (Kappa = 0·66) and of intrauterine growth retardation (Kappa = 0·48).

There have been a number of reports suggesting a clinical value of fetal blood flow assessment using Doppler ultrasound. Fetal blood flow has been assessed in normal and high risk pregnancies, in various vessels, and using a variety of techniques Pulsed Doppler and imaging ultrasound are used for assessing flow in the fetal aorta (Jouppila & Kirkinen 1984*a*; Lingman & Maršál 1986*a*) and in the umbilical vein (Gill *et al.* 1984), and both pulsed wave (Reuwer *et al.* 1984) and continuous wave Doppler (Trudinger *et al* 1985) are utilized for blood velocity waveform assessments in the umbilical arteries.

Intrauterine fetal blood flow estimation by pulsed Doppler and imaging ultrasound has been assessed as a method of antenatal surveillance in high risk pregnancies at the Department of Obstetrics and Gynaecology, Malmo, during recent years Earlier reports from the Department described the fetal aortic and umbilical volume blood flow and fetal aortic waveform analysis in normal pregnancies (Lingman & Maršál 1986 *a,b*) and in pregnancies complicated by intrauterine growth retardation (IUGR) (Laurin *et al.* 1987). Here we present an evaluation of the capacity of fetal blood flow assessment to predict IUGR and fetal outcome, when used as a diagnostic test in a group of pregnancies where growth retardation was suspected on the basis of ultrasound screening.

Subjects and methods

The current ultrasound screening programme at the Department includes measurement of the

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fetal biparietal diameter (BPD) at 16 weeks gestation to date the pregnancy and measurement of BPD and the mean of two orthogonal abdominal diameters (AD) at 32 weeks gestation to assess fetal growth. This screening enabled selection of an IUGR risk group of 159 patients. By comparing the fetal measurements obtained at the second examination, with reference values for gestational age established for the Malmö population (Persson & Weldner 1986), a predicted birthweight deviation was calculated. IUGR was suspected when the predicted birthweight deviation was ≥1·5 SD below the mean. A newborn with a birthweight of ≥2 SD below the mean birthweight for gestational age in the population was classified as IUGR.

Intrauterine fetal blood flow was measured within a week after the ultrasound fetometry in all pregnancies where IUGR was suspected. The fetometry and the fetal blood flow measurement were repeated at intervals of 2 weeks. Fetal blood flow was assessed in the thoracic descending aorta and in the intra-abdominal part of the umbilical vein, using the pulsed wave Doppler technique and imaging ultrasound (Eik-Nes *et al.* 1984). The 2 MHz Doppler transducer and the real-time linear array transducer are attached to each other at an angle of 45°. When the real-time transducer is parallel to the vessel under examination, the insonation angle is 45°. The distance from the Doppler transducer to the vessel is measured on the screen, and the sample volume of the Doppler instrument is positioned accordingly. The Doppler shift signals are controlled by ear, the spectrum is analysed on-line and displayed on an oscilloscope for visual control. The Doppler signals pass through a 100 Hz high-pass filter.

The mean blood velocity (V) and the vessel diameter (d) are required for calculating volume blood flow (Q):

$$Q = V \pi d^2/4 \cos 45°$$

Vessel diameter (d) is measured on the screen by electronic caliper, and calculated as the mean of 10 consecutive measurements of frozen vessel images (Eik-Nes *et al.* 1984) At each blood flow examination, fetal weight is estimated by ultrasound fetometry (Persson & Weldner 1986) and volume blood flow related to it (ml/min/kg).

The waveform analysis was performed on the fetal aortic maximum blood velocity curve. Pulsatility index (PI) (Gosling *et al.* 1971) and the rising slope (RS) (McCallum 1981) were calculated by minicomputer as mean values over 10 consecutive heart cycles (Fig. 1). Only technically satisfactory readings obtained during fetal apnoea and quiescence were analysed.

Based on the findings of a pilot study (unpublished), four semi-quantitative 'blood flow classes' (BFC), 0–III, were formed by combining the PI and the shape of the diastolic part of the velocity curve. BFC 0 indicates a normal PI and a normal blood flow velocity curve with a positive flow throughout the cardiac cycle BFC I is characterized by a positive flow throughout the cardiac cycle, but an increased PI (≥ mean + 2 SD). BFC II indicates that the end-diastolic flow is not detectable. The criterion for BFC III is either the absence of a positive flow during the main part of the diastole, or the presence of a reversed flow (Laurin *et al.* 1987).

On the basis of reference values obtained from a longitudinal study of normal pregnancies from the same population (Lingman & Maršál 1986*a*,*b*), the blood flow variables were divided into 0·5 SD groups, starting from the mean, forming cut-off values. For the BFC, the classes I-III were used as cut-offs.

The fetal outcome variables were IUGR *v.* non-IUGR, operative delivery for fetal distress (ODFD) (Sykes *et al.* 1983) *v.* non-ODFD, Apgar scores at 1 and 5 min, and umbilical vein and artery pH. ODFD includes emergency caesarean section and vacuum or forceps extrac-

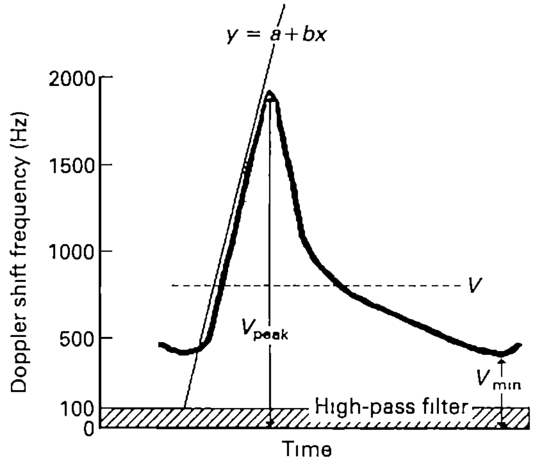

Fig. 1. A normal fetal aortic blood velocity curve showing the velocity waveform entities and the level of the high pass filter. V_{peak}, peak velocity, V, mean velocity over the cardiac cycle; V_{min}, the least diastolic velocity

$$\text{Pulsatility index (PI)} = \frac{V_{peak} - V_{min}}{V},$$

$$\text{rising slope (RS)} = \frac{b}{V}$$

Table 1. Evaluation of a diagnostic test*

Test result	Actual condition	
	Present	Absent
Positive	a (true positives)	b (false positives)
Negative	c (false negatives)	d (true negatives)

$n = a+b+c+d$

Sensitivity $= a/(a+c)$

Specificity $= d/(b+d)$

Positive predictive value $= a/(a+b)$

Negative predictive value $= d/(c+d)$

Prevalence $= (a+c)/(a+b+c+d)$

Kappa index $= (\mathrm{Po}-\mathrm{Pe})/(1-\mathrm{Pe})$

$\mathrm{Po} = (a+d)/n,$

$\mathrm{Pe} = [(a+b)(a+c)/n+(c+d)(b+d)/n]/n = [(a+b)(a+c) + (c+d)(b+d)]/n^2$

* Modified after Grant & Mohide (1982).

tion, on signs of imminent fetal distress as judged by cardiotocographic changes, e.g. late or variable decelerations, or silent pattern (<5 beats/min). An Apgar score of ≤ 7 at 1 and 5 min, an umbilical artery pH $\leq 7{\cdot}10$ and umbilical vein pH $\leq 7{\cdot}20$ were classified as abnormal.

A total of 277 blood flow examinations were performed, but only the final examination before delivery is discussed here. Throughout the study, the results of the blood flow measurements were not made available to the clinicians in charge.

Statistical methods

The efficacy of the fetal blood flow variables to indicate fetal outcome was evaluated in terms of sensitivity and specificity (Table 1), as reflected in receiver operating characteristic (ROC) curves (Richardson *et al.* 1985). The ROC curve is a plot of the sensitivity on the false positive rate (1-specificity) for a test, at different cut-off points. Since abnormal values for blood flow variables change in the degree of abnormality as the cut-off level is changed, the efficacy of the variables in predicting abnormal fetal outcome can be evaluated. Test characteristics (sensitivity and specificity) were calculated for each cut-off level in 0·5 SD steps from the normal mean value towards abnormality.

To compare the different test variables, Cohen's Kappa index (Grant & Mohide 1982) was calculated (Table 1). Kappa values below 0·20 indicate agreement only by chance; values between 0·20 and 0·80 reflect fair to good agreement and a value of 1·00 would reflect a perfect agreement between the test variable and actual condition (Grant & Mohide 1982).

Results

Figure 2 shows the distribution of birthweight deviations in each of the four blood flow classes. The ROC curves in Figures 3–6 show the efficacy of the blood flow variables, in terms of sensitivity and false positive rate, as markers for the occurrence of IUGR, ODFD, an Apgar score of ≤ 7 at 1 min, and an umbilical vein pH$\leq 7{\cdot}20$. BFC

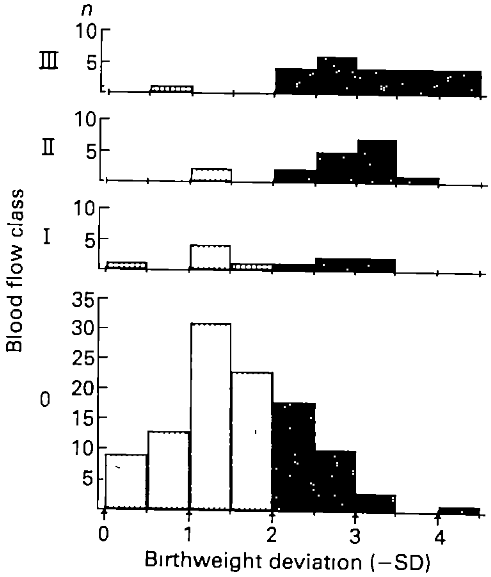

Fig. 2. Distribution of birthweight deviation by blood flow class. Intrauterine growth retardation defined as birthweight $\geq$2SD below the mean (dark columns).

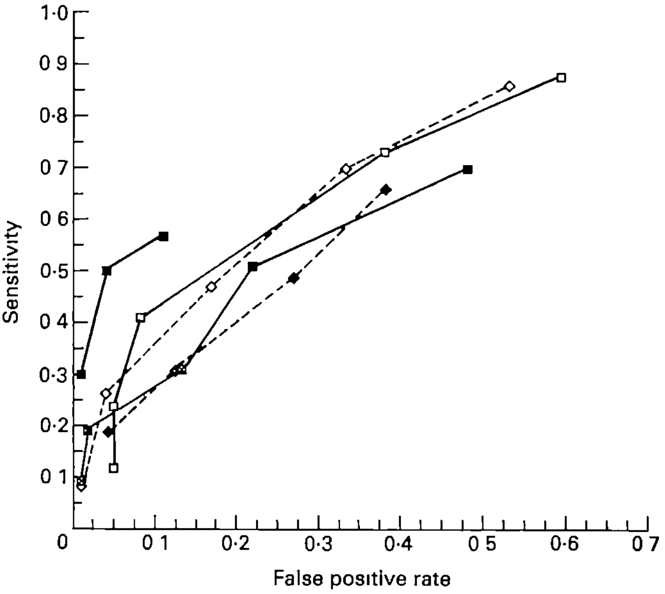

Fig. 3. Receiver operating characteristic (ROC) curves showing the sensitivity and false positive rate for various blood flow variables in the prediction of intrauterine growth retardation (■) Blood flow class; (□) pulsatility index; (⊠) rising slope; (◈) volume flow in the fetal thoracic aorta; (◇) volume flow in the umbilical vein.

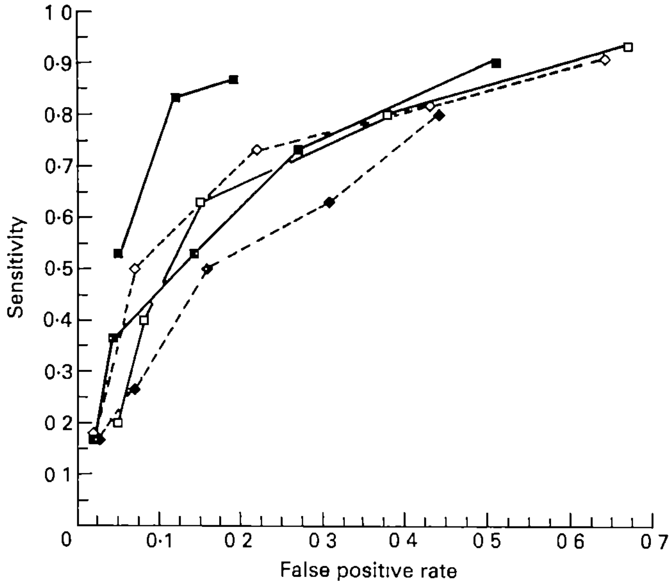

Fig. 4. Receiver operating characteristic curves showing the sensitivity and false positive rate for various blood flow variables in the prediction of operative delivery for fetal distress. For explanation of the symbols see Fig 3

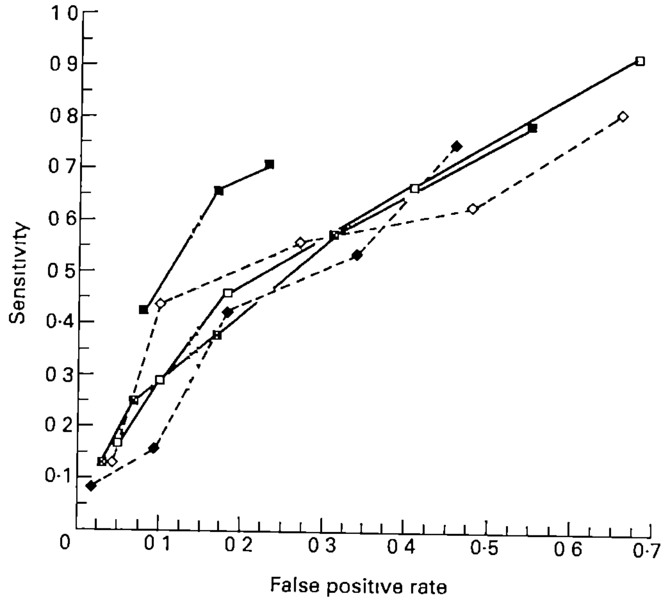

Fig. 5. Receiver operating characteristic curves showing the sensitivity and false positive rate for various blood flow variables in the prediction of 1-min Apgar score ≤7. For explanation of the symbols see Fig 3

proved to be the most powerful variable in predicting fetal outcome.

The prevalence of IUGR in the study group was 74/159 = 46·5%. The prevalence figures of the variables describing fetal outcome are given at the bottom of Table 2, which also gives the

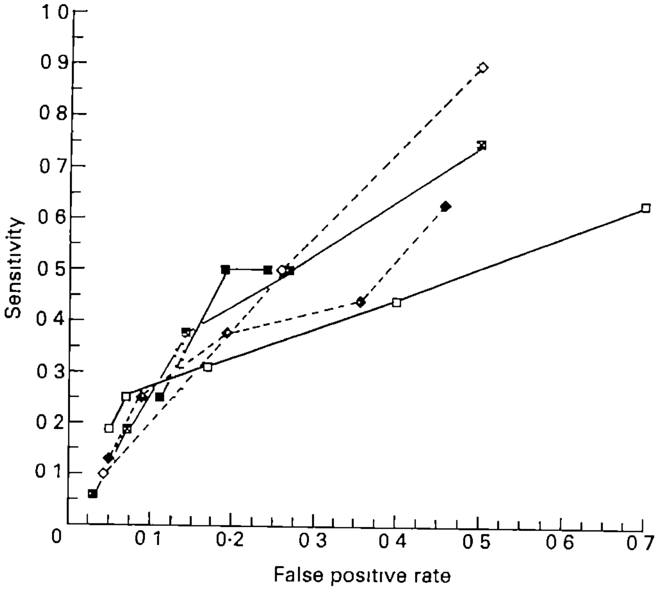

Fig. 6. Receiver operating characteristic curves showing the sensitivity and false positive rate for various blood flow variables in the prediction of an umbilical vein pH ≤7·20 For explanation of the symbols see Fig 3

Table 2. Cohen's Kappa values for the blood flow variables in predicting fetal outcome. Prevalence of the outcome variables

	Fetal outcome variable†					
			Low Apgar score		Low umbilical pH	
Blood flow variable*	IUGR	ODFD	1 min	5 min	Artery	Vein
PI	0·36	0·44	0·21	0·21	0·05	0·21
RS	0·29	0·40	0·21	0·13	0·10	0·21
BFC	0·48	0·66	0·40	0·12	0·12	0·24
Q Ao	0·28	0·34	0·20	0·10	0·07	0·15
V	0·43	0·46	0·38	0·08	0·06	0·08
V_{peak}	0·17	0·13	0·11	0·07	0·18	0·14
V_{min}	0·49	0·51	0·32	0·10	0·09	0·21
Q Vu	0·36	0·45	0·32	0·23	−0·03	0·09
Vu	0·18	0·30	0·18	0·16	−0·07	0·05
Prevalence	74/159	30/156	24/156	5/156	9/95	16/116
	0·47	0·19	0·15	0·03	0·09	0·14

* PI, Pulsatility index; RS, rising slope; BFC, blood flow class, Q Ao, volume flow in fetal thoracic aorta, V_{peak}, peak velocity, V, mean velocity over the cardiac cycle, V_{min}, the least diastolic velocity, Q Vu, volume flow in the umbilical vein, V, mean velocity in the umbilical vein.

† IUGR, intrauterine growth retardation, ODFD, operative delivery for fetal distress; low Apgar score ≤7 at 1 and 5 min; low pH ≤7·10 in the umbilical artery and ≤7·20 in the vein

Kappa values at the most effective cut-off points for each of the fetal blood flow variables in predicting fetal outcome.

The efficacy of Doppler blood flow to predict IUGR and ODFD respectively is given in Table 3. BFC 0–I was considered as normal and BFC II–III as abnormal.

Discussion

An IUGR risk group was selected on the basis of ultrasound fetometric screening in the third trimester. Non-invasive fetal blood flow assessment by pulsed Doppler ultrasound was then used as a diagnostic test to predict the occurrence of an abnormal result in the fetal outcome variables (Tables 2 and 3). Although this is straightforward in theory, in reality normal and abnormal cannot be unequivocally differentiated. In this study, for instance, fetal birthweight ≥2SD below the mean served as a definition of IUGR, which is, of course, an approximation, since obviously a genetically small infant would be incorrectly classified as IUGR. Similarly, an infant genetically 'programmed' to have a birthweight above the mean, would be classified as non-IUGR, as long as the birthweight was above mean −2 SD, even if the infant was significantly growth retarded. Reference to standard weight curves might be equivocal in such cases. The indications for ODFD are certain typical cardiotocographic changes, though an abnormal fetal heart rate pattern is not inevitably a marker of fetal hypoxia. Similar objections can be raised both with regard to Apgar score and umbilical pH as markers. In clinical obstetrics, however, we must accept such imperfections and treat the outcome variables as if they indeed reflected actual conditions.

The diagnostic method (i.e. pulsed Doppler assessment of fetal aortic and umbilical venous blood flow) has methodological pitfalls (Eik-Nes *et al.* 1984), although most, but not all, can be avoided by evaluating the circulatory state of the fetus in terms of waveform analysis rather than volume blood flow. The waveform analysis is performed on the maximum velocity curve, i.e. the Doppler shift spectrum envelope, because the maximum velocity is less sensitive to non-uniform insonation of the vessel than is the mean velocity used for volume flow evaluation (Lingman & Maršál 1986*b*). The detection of the correct maximum velocity signal is facilitated by using a relatively large Doppler sample volume The Doppler shift signals pass through a high-pass filter of 100 Hz to remove low frequency noise, e.g. originating from the vessel wall movements (Fig. 1). However, the high-pass filter also removes slow blood velocities, which

Table 3. Efficacy of the ultrasound Doppler flow measurements to predict IUGR (upper half) and the occurrence of operative delivery for fetal distress (ODFD) (lower half) in the IUGR risk group. (The cut-off point for BFC is the same as used in Table 2)

		IUGR		
	Fetal blood flow	Present	Absent	Total
	BFC II–III	37	3	40
	BFC 0–I	37	82	119
	Total	74	85	159
Sensitivity. 50·0%		Positive predictive value· 92·5%		
Specificity. 96·5%		Negative predictive value· 68 9%		
Prevalence· 47%		Kappa index 0·48		

		ODFD		
	Fetal blood flow	Present	Absent	Total
	BFC II–III	25	13	38
	BFC 0–I	5	113	118
	Total	30	126	156
Sensitivity. 83·3%		Positive predictive value· 65 8%		
Specificity· 89 7%		Negative predictive value· 95·8%		
Prevalence 19·2%		Kappa index. 0 66		

IUGR, Intrauterine growth retardation, ODFD, operative delivery for fetal distress, BFC, blood flow class (please see text).

might be critical when fetuses with impaired circulation are examined. As shown in Fig. 7, 100 Hz corresponds to a velocity of 5·4 cm/s, at an insonation angle of 45°. A blood velocity of up to 44 cm/s might not be detectable and might thus be interpreted as zero flow when the insonation angle is increased and the high-pass filter present. In the present study, in all instances of values indicating absence of diastolic flow (zero flow), the insonation angle was re-checked.

The highest Kappa values were found in the prediction of IUGR and ODFD. This was to be expected, mainly because IUGR and ODFD had the highest prevalence of the four outcome variables (Table 2), and the Kappa value is dependent on the prevalence (Grant & Mohide 1982). The prevalence of IUGR in the risk group, 47%, should be compared with that of 3·8% for the total population of Malmo. Although the prevalence of ODFD was lower than that of IUGR, the Kappa values were higher in predicting ODFD. This means that the fetal circulation was in fact compromised in most of those with ODFD, and not compromised in many of those with IUGR. A low Apgar score does not necessarily imply that fetal circulation

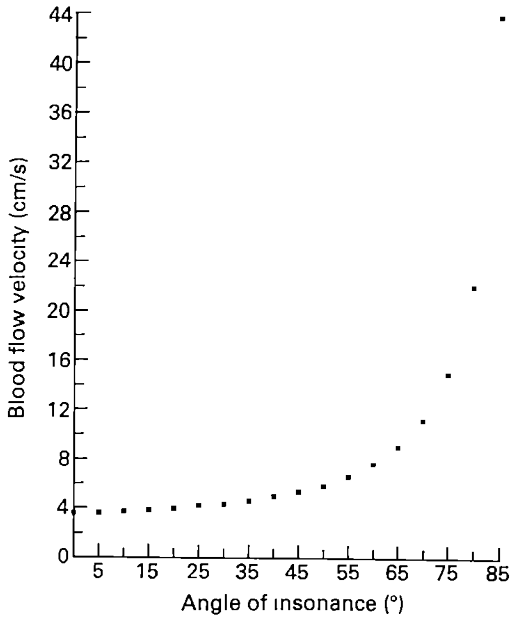

Fig. 7. Effect of a 100 Hz high-pass filter on the blood velocity Doppler signals, the dots indicate the maximum possible errors in blood velocity measurement at various insonation angles

has been impaired during intrauterine life, but might instead be the result of stress during delivery, to which the IUGR fetus is more vulnerable than is the non-IUGR fetus (Lin *et al.* 1980). The low prevalence adds to the difficulty of predicting low 1 or 5 min Apgar scores, or predicting low pH values in the cord blood. Since the values of prevalence of a low umbilical artery pH and a low Apgar at 5 min were very low, these outcome variables have not been included in the ROC curves shown in Figs 3–6.

As judged by the Kappa index, the single most efficient blood velocity variable was the least diastolic velocity (V_{min}). This is in accordance with earlier reports, both by Jouppila & Kirkinen (1984*a*) and from this Department (Lingman *et al.* 1986; Laurin *et al.* 1987). Since the more complex variable, PI, includes peak velocity (V_{peak}), mean velocity over the cardiac cycle (V), and least diastolic velocity (V_{min}) (Fig. 1), it generally gave lower Kappa values than did V_{min} alone, owing to the very low Kappa values for V_{peak}. Nevertheless, PI had a better Kappa value than did V_{min}, for predicting a low 5-min Apgar score (Table 2). RS was a slightly weaker predictor of fetal outcome than was PI.

The low Kappa values found for the volume flow in the fetal descending aorta (Q Ao) is probably explained by an overestimation of the Q Ao values due to underestimation of fetal weight, giving fewer low Q Ao values and, as a consequence, a lower discriminatory capacity. Even though the same error in weight estimation also affects the estimation of volume flow in the umbilical vein, this proved to be a reasonably efficacious variable in predicting both IUGR, low Apgar score, and ODFD. This is in agreement with earlier reports (Gill *et al.* 1984; Jouppila & Kirkinen 1984*b*; Lingman *et al* 1986).

The new semi-quantitative entity, BFC, was generally the best predictor of fetal outcome. The most effective cut-off level was BFC II, meaning that BFC 0–I was considered as normal and BFC II–III as abnormal. When calculating the Kappa values given in Table 2, BFC II was used as cut-off point. BFC II includes the end-diastolic absence of flow and might be compared to a very low V_{min} The occurrence of BFC II–III strongly indicated ODFD (Table 3), and was also a fairly good indicator both of IUGR (Table 3) and of a low 1-min Apgar score. Figure 2 shows the distribution, for each BFC, of infants having birthweight ⩾2 SD below the mean, which was the definition of IUGR adopted in the study. It would perhaps be more appropriate to label small fetuses with a normal BFC (BFC 0) as small-for-gestational-age, and those with a compromised circulation as IUGR.

There were three intrauterine deaths which were excluded when ODFD and Apgar scores were evaluated. Two of the fetuses were classified as IUGR and of BFC III at the last examination before they died *in utero*, 1 and 2 weeks before death. The third fetus was classified as BFC I a week before death, and had a weight deviation of −1·5 SD at birth. Had this been an open study, of course, the finding of an abnormal fetal blood flow would have initiated clinical measures and two of these fetuses might have been saved. Perinatal mortality in the study group was 1·9% compared with 0·6% in the general population.

Since the Doppler velocity curve (Fig. 1) provides a very large amount of information, the use of a single variable to characterize the waveform would therefore seem to be insufficient. However, in the absence of more sophisticated, computerized multifactorial pattern recognition procedures in Doppler blood velocity waveform analysis (Evans & Caprihan 1985), BFC is a fairly easy method of approximate waveform evaluation. Furthermore, the results presented in Table 3 imply that the picture of the fetal circulatory state, as obtained by determining whether there is a forward flow throughout diastole (BFC 0–I *v.* BFC II–III), is efficient in the prediction both of IUGR and of ODFD.

This study demonstrates clinical usefulness of the non-invasive intrauterine fetal aortic blood flow measurement in the surveillance of high risk pregnancies. When applied as a diagnostic tool to a risk group preselected by means of ultrasound screening, waveform analysis using BFC efficiently predicts imminent fetal asphyxia, the Kappa value being 0·66. The Kappa value for the prediction of IUGR was 0·48, which is equal to the Kappa value obtained in repeated ultrasound screening for IUGR in the same population (Laurin & Persson 1987). We do not yet know for how long a normal blood flow result is valid, and the appropriate time interval between examinations can thus not be settled. This question remains and requires still more experience.

To conclude, we consider ultrasound assessment of fetal blood flow with waveform analysis to be a powerful clinical tool for use in the surveillance of high risk pregnancies, and a valuable aid in the antenatal diagnosis of IUGR

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Received 22 September 1986
Accepted 24 February 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp. 949–955

Menstrual regulation by intramuscular injections of 16-phenoxy-tetranor PGE_2 methyl sulfonylamide or vacuum aspiration. A randomized multicentre study

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Summary. A multicentre trial was conducted to compare the efficacy and side-effects of an intramuscularly administered PGE_2 analogue and vacuum aspiration in women with a delay of up to 21 days in the expected onset of menses. A total of 473 such women were randomly allocated to treatment with either 16-phenoxy-W-17, 18, 19, 20-tetranor PGE_2 methyl sulfonylamide (three intramuscular injections of 0·5 mg at 3-h intervals) or vacuum aspiration, and the outcome of therapy assessed 1, 2 and 6–8 weeks later. Retrospective analysis of hCG levels indicated that 419 (88·6%) women had been pregnant at the time of treatment. With few exceptions, administration of the PGE_2 analogue induced vaginal bleeding in both pregnant and non-pregnant women but the duration and subjectively perceived amount of bleeding were greater than after vacuum aspiration. Both treatments were equally effective. In pregnant women the overall frequency of complete abortion was 91% for prostaglandin treatment and 94% for vacuum aspiration. If non-pregnant women were included, the respective success rates (i.e. percentages of women not pregnant 2 weeks after treatment) were 92% and 95%. Gastrointestinal side-effects and lower abdominal pain requiring intramuscular analgesia were more common after prostaglandin therapy than following vacuum aspiration in both pregnant and non-pregnant women.

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The technique for early abortion referred to as 'menstrual regulation' has been promoted in the belief that its simplicity, low cost and minimal complications would lend itself to widespread use. For pregnancies of less than 49 days' amenorrhoea, vacuum aspiration has been performed using small cannulae that do not require dilatation of the cervix. In order to reduce the risk of uterine perforation, disposable flexible cannulae have been employed instead of rigid metal ones. Experience suggests, however, that the use of small cannulae is not without problems, in particular incomplete evacuation of the uterus and continuation of the pregnancy. In a WHO multicentre study, the frequency of these complications was 4·9% and 3·7%, respectively (WHO 1979) This means that the procedure, although often regarded as simple, requires skilled and experienced surgeons.

A medical method for menstrual regulation would therefore be an attractive alternative, provided the procedure is safe for both pregnant and non-pregnant women and results in a high frequency of complete abortion. Such a procedure could be administered in the outpatient department or even be self-administered. So far, prostaglandins (PG) are the only compounds with this potential which have been investigated clinically on a large scale. An alternative is the use of steroids with anti-progestational activity, a therapy which is in the initial stage of clinical assessment (Herrmann *et al.* 1982; Kovacs *et al* 1984; Bygdeman & Swahn 1985).

The use of prostaglandins is based on their unique ability to stimulate uterine contractility and induce abortion, even during very early pregnancy. The initial trials using PGE_2 and $PGF_{2\alpha}$ were on the whole discouraging. The only effective route was intrauterine administration and premedication was necessary to reduce the frequency of side-effects (see Bygdeman 1979 for references). The situation has changed, at least partly, with the introduction of prostaglandin analogues. Intrauterine administration of different analogues has been shown to be highly effective in terminating early pregnancy (Karim *et al.* 1977*a*; Takagi *et al.* 1977), and encouraging results have also been reported for certain PGE analogues that have an increased stability in suppository form or in formulation for intramuscular injection. To this group belong 16, 16-dimethyl-trans-Δ^2-PGE_1 methyl ester (16,16-dimethyl PGE_1), 9-deoxo-16,16-dimethyl-9-methylene PGE_2 (9-methylene PGE_2) and 16-phenoxy-W-17,18,19,20-tetranor PGE_2 methyl sulfonylamide (PGE_2 methyl sulfonylamide). The first two compounds are administered vaginally, the third one by intramuscular injection.

Several clinical studies have shown that highly effective dose schedules resulting in a frequency of complete abortion of over 90% can be used for all three analogues. Side-effects were limited to occasional vomiting and diarrhoea in approximately 50% of the patients and uterine pain necessitating analgesic therapy in approximately 30% of the patients (Takagi *et al.* 1978; Karim *et al.* 1977*b*, Bygdeman *et al.* 1983). One of these analogues, 9-methylene PGE_2, was compared with vacuum aspiration. Both procedures were found equally effective in terminating early pregnancy (Bygdeman *et al.* 1983).

The aim of the present study was to compare the efficacy and safety of one of these PGE analogues, PGE_2 methyl sulfonylamide, with vacuum aspiration in a large group of patients with amenorrhoea of 49 days or less. Since a positive hCG test was not a prerequisite for entering the study, the outcome of both procedures in non-pregnant women with a delay of menstruation due to reasons other than pregnancy could also be assessed.

Patients and methods

Ethical approval for the study was obtained from WHO's Secretariat Committee for Research into Human Subjects and from the corresponding ethics committees in the participating institutions.

Criteria for admission to the study included at least one previous full-term pregnancy, duration of amenorrhoea of up to 49 days, a normal general and gynaecological history and examination, and giving informed consent that either a

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surgical or a medical treatment was to be used to induce 'menstruation'.

In total, 486 women fulfilling the above listed criteria were recruited in the 12 centres participating in the study. Thirteen subjects were excluded due to protocol violations Thus, the outcome of therapy was assessed in 473 women

All women were admitted to the hospital on the day of treatment for at least 8 h. On admission a urine sample for hCG testing or blood sample for β-hCG assay was obtained for retrospective classification of the subjects as pregnant or non-pregnant.

The treatment was either a surgical or a non-surgical procedure and the allocation of the individual patient was based on a computer-generated random table and sealed envelopes. Patients in the non-surgical group received 0·5 mg PGE_2 methyl sulfonylamide by intramuscular injection three times at 3-h intervals. The patients in the surgical group were treated with vacuum aspiration, usually under local anaesthesia. Vital signs and body temperature were recorded at regular intervals. The onset of bleeding, uterine pain and side-effects were noted whenever they occurred.

The protocol included three follow-up visits at 1, 2 and 6–8 weeks after treatment. In subjects with a positive hCG test in blood or urine on the day of treatment a first assessment of the outcome of therapy (complete abortion, incomplete abortion or continuing pregnancy) was made at the second follow-up visit. This assessment was based on the duration and amount of bleeding, the pattern of plasma β-hCG decrease or the urinary pregnancy test, gynaecological examination and, if necessary and available, ultrasound examination. Intervention before the second follow-up visit was not allowed unless clinically indicated, e g. for heavy bleeding. In such cases, the outcome was classified as an incomplete abortion. If the patient was still pregnant at the second follow-up visit, the pregnancy was terminated by vacuum aspiration. If it was doubtful whether the abortion was complete or incomplete, the assessment awaited the third follow-up visit provided that significant bleeding did not occur. If curettage was necessary during the time from the second follow-up visit to the first menstruation, the outcome of therapy was based on histological examination. If products of conception were found in the curettings, the outcome was classified as incomplete abortion. The duration and amount of bleeding and the appearance of complications were noted at each follow-up visit and summarized at the last follow-up visit. At that time, the onset and characteristics of the first menstruation were also recorded.

Results

Of the 473 women included in the study, 419 were pregnant while 54 (11·4%) were not pregnant at the time of treatment. The data presented in Table 1 show that the non-pregnant and pregnant patients were equally distributed between the two treatment groups. Important characteristics such as gravidity, parity, duration of amenorrhoea, age, height and weight, were also similar in the different groups.

Vacuum aspiration and intramuscular administration of PGE_2 methyl sulfonylamide were found to be equally effective in terminating early pregnancy. The overall frequency of complete abortion was 91·1% for prostaglandin and 94·0% for vacuum aspiration (Table 2). The figures for incomplete abortion and pregnancy continuation were 7·4% and 1·5% for prostaglandin and 2·8% and 3·2% for vacuum aspiration, respectively. If the non-pregnant patients were included, the frequency of 'successful treatment' (i.e. not pregnant at the second follow-up visit) was 92·1% for prostaglandin and 94·7% for vacuum aspiration.

The outcome of therapy was similar for prostaglandin treatment and vacuum aspiration in all but four of the 12 centres (Table 3). If the two centres with a lower 'success rate' for either prostaglandin (numbers 7 and 10) or vacuum aspiration (numbers 2 and 4) were excluded, the overall success rate increased to 96·3% for prostaglandin and to 98·0% for vacuum aspiration.

The frequency of complete abortion following prostaglandin therapy was unrelated to duration of amenorrhoea within the protocol range of 4–7 weeks. For vacuum aspiration, significantly more failures were found between days 43–49 than between days 29–42 of amenorrhoea (Table 4).

Generally, the patients started to bleed 2–8 h after the start of prostaglandin administration in both the pregnant and non-pregnant groups. In the former—but not in the latter—group the (geometric) mean duration of bleeding after prostaglandin administration was significantly

Table 1. Patient characteristics

Characteristic	Prostaglandin treatment		Vacuum aspiration	
	Non-pregnant	Pregnant	Non-pregnant	Pregnant
No. of patients (%)	25 (5·3%)	203 (43·0%)	29 (6·1%)	216 (45·6%)
Duration of amenorrhoea (days)	40·7 (3·8)	42·1 (2·8)	40·5 (2·7)	42·1 (2·9)
Gravidity	2·0 (1·1)	3·5 (1·5)*	2·3 (1·4)	3·7 (1·7)*
Parity	1·2 (0·5)	1·7 (1·0)	1·3 (0·8)	1·8 (1·1)
Weight (kg)	56·0 (8·3)	55·4 (9·1)	54·3 (7·7)	55·2 (9·5)
Height (cm)	159 (6)	160 (7)	158 (8)	159 (7)
Age (years)	31·5 (6·1)	30·7 (5·6)	30·1 (6·2)	31·0 (5·6)

* Including the present pregnancy.
Results are means (SD) where appropriate.

Table 2. Efficacy of treatment

	Prostaglandin treatment		Vacuum aspiration	
	Non-pregnant	Pregnant	Non-pregnant	Pregnant
No. of patients	25	203	29	216
Complete abortion	—	185* (91·1%)	—	203* (94·0%)
'Successful treatment'†	210 (92·1%)		232 (94·7%)	
Incomplete abortion	—	15 (7·4%)	—	6 (2·8%)
Pregnancy continuation	—	3 (1·5%)	—	7 (3·2%)
Total	228		245	

* Numbers include patients in whom no products of conception were found at curettage during the follow-up period (two women in prostaglandin group and one woman in vacuum aspiration group).

† Represents women not pregnant at second follow-up visit, i.e. sum of non-pregnant subjects and pregnant women with complete abortion

longer than after vacuum aspiration (Table 5). The amount of blood loss was subjectively assessed by the patients in relation to their own menstruation. In the vacuum aspiration group, 92·6% of the pregnant patients regarded the blood loss to be equal to or less than their menstruation. Only 1·4% of these patients regarded the blood loss to be much more. The corresponding figures for pregnant patients treated with prostaglandin were 56·0% and 6·2% respectively (Table 5). The judgement of the non-pregnant patients with regard to amount of blood loss was similar to that of the pregnant patients except that none of these patients estimated the blood loss to be much more than the normal period.

Occasional episodes of vomiting and diarrhoea occurred in between 20% and 30% of the patients treated with prostaglandin, irrespective of whether they were pregnant or not. The corresponding figures for the patients undergoing vacuum aspiration (between 0% and 2%) were significantly lower ($P<0{\cdot}001$) (Table 6).

It is difficult to compare the degree of pain between the surgical and non-surgical procedure because most patients in the surgical group received analgesia at operation. Only 1 out of 245 patients needed an additional injection during the postoperative period. In the prostaglandin treated patients, the pain was due to stimulation of uterine contractility and generally lasted for 3–4 h; 12% of the pregnant and 4% of the non-pregnant women received an analgesic injection (generally meperidine chloride).

The characteristics of the first menstruation after treatment were recorded in 421 patients (89%). Menses started at approximately the same time, after 5·1 to 5·5 weeks, in all four groups and, in the majority of patients, was similar to their normal menstruation both with regard to duration of bleeding and perceived amount of blood loss.

Table 3. Total number of patients and number and percentage of 'successfully' treated patients in different centres (includes both pregnant and non-pregnant patients)

Centre	No of patients	Prostaglandin treatment No	Prostaglandin treatment %	Vacuum aspiration No.	Vacuum aspiration %
1	40	20/20	100	20/20	100
2	26	11/11	100	12/15	80·0
3	30	15/15	100	14/15	93·3
4	59	22/24	91·7	29/35	82·9
5	59	29/30	96·7	28/29	96·6
6	30	14/15	93·3	14/15	93·3
7	56	21/28	75 0	27/28	96·4
8	60	29/30	96·7	30/30	100
9	30	14/15	93·3	15/15	100
10	29	10/14	71·4	15/15	100
11	30	15/15	100	15/15	100
12	24	10/11	90·9	13/13	100
Total	473	210/228	92·1	232/245	94·7

Table 4. Outcome of therapy in relation to duration of amenorrhoea in pregnant patients

	Prostaglandin treatment 29–42 days	Prostaglandin treatment 43–49 days	Vacuum aspiration 29–42 days	Vacuum aspiration 43–49 days
No. of patients	123	80	140	76
Complete abortion*	111 (90·2%)	74 (92·5%)	136 (97·1%)	67 (88·2%)
Incomplete abortion	9	6	1	5
Pregnancy continuation	3	0	3	4

* χ^2-tests; prostaglandin therapy: $\chi^2=0{\cdot}31$, df=1, $P=0{\cdot}6$; vacuum aspiration: $\chi^2=7{\cdot}03$, df=1, $P<0{\cdot}01$.

Complications during the post-treatment period, besides curettage due to pregnancy continuation or incomplete abortion, were few. Out-patient or hospital treatment with antibiotics for signs of pelvic infection was given to eight patients (3·5%) treated with prostaglandin and to four patients (1·6%) undergoing vacuum aspiration.

Discussion

There is at present interest in developing medical methods for terminating pregnancy as an alternative to surgical procedures. Since 1971, when the first report on the clinical use of prostaglandins for termination of early pregnancy was published (Karim 1971), the efficacy and safety of prostaglandin administration have been significantly improved. Studies on the last generation of vaginally or intramuscularly administered PGE analogues, 16,16-dimethyl-PGE_1, 9-methylene-PGE_2 and PGE_2 methyl sulfonylamide, have reported a frequency of complete abortion around 95% if the treatment is given during the first 3 weeks after a missed menstrual period (Takagi *et al.* 1978; Karim *et al.* 1977*b*; Bygdeman *et al.* 1983). In small randomized studies, vaginal or intrauterine administration of prostaglandins has been shown to be as effective as vacuum aspiration if performed during the same period of gestation (Ragab & Edelman 1976; Lundstrom *et al* 1977; Rosén *et al.* 1984), but, until now, it has been difficult to reproduce these results in multicentre studies. In one such study, involving 11 centres and 358 early pregnant patients, the frequency of complete abortion following vaginal administration of 16,16-dimethyl-PGE_1 was 86% but there was considerable between-centre variation (WHO 1982). In the five most successful centres, the mean frequencies of complete abortion,

Table 5. Duration and amount of bleeding following vacuum aspiration (VA) or prostaglandin (PG) treatment

	Pregnant		Non-pregnant	
	VA	PG	VA	PG
Duration of bleeding (days) (geometric mean and 95% confidence intervals)*	3·7 (2·6–5·4)	8·9 (8·0–9·8)	2·6 (2·0–3·3)	3·8 (2·5–5·8)
Amount compared to own menstruation† (% of patients)				
Less	72·2	16·6	71·4	39·1
Equal	20·4	39·4	25·0	26·1
More	6·0	37·8	3·6	34·8
Much more	1·4	6·2	0·0	0·0
Total	100·0	100·0	100·0	100·0
Number of respondents	216	193	28	23

* Two-sample t-tests on log data; pregnant patients. t=11·14, df=412, P<0·001, non-pregnant patients: t=1·62, df=50, P=0·11

† χ^2-tests; pregnant patients: χ^2=136·7, df=3, P<0·001, non-pregnant patients· χ^2=9·3, df=2, P=0·04

incomplete abortion and failure of treatment were 93·5%, 4·3% and 2·2%, respectively. These figures are similar to those reported for vacuum aspiration if performed during early pregnancy.

The present multicentre study, which involved random assignment of pregnant patients (duration of amenorrhoea of up to 49 days), indicates that intramuscular administration of PGE_2 methyl sulfonylamide and vacuum aspiration were equally effective: the frequency of complete abortion was 91·1% and 94·0%, respectively. If the non-pregnant patients were included, the frequency of 'successful treatment' (not pregnant at the second follow-up visit) increased to 92·1% for prostaglandin treatment and to 94·7% for vacuum aspiration.

In contrast to the previous WHO multicentre study of vaginally administered 16,16-dimethyl-PGE_1 (WHO 1982), the between-centre variation in the present study was small. The reason may be the different routes of administration. Intramuscular administration is likely to be less susceptible to failure than vaginal administration in which leakage of the compound from the vagina may occur. In the present study a success rate between 90% and 100% for both treatments was achieved by 8 of the 12 centres; in the remaining four centres the success rate for either prostaglandin treatment or vacuum aspiration was significantly lower. If these 'unusual' centres were excluded the frequency of 'successful treatment' increased to 96·3% for prostaglandin treatment and to 98·0% for vacuum aspiration.

Prostaglandin therapy was associated with a higher frequency of gastrointestinal side-effects and a longer and heavier period of bleeding after treatment compared with vacuum aspiration. However, the intensity of the gastrointestinal side-effects was rarely severe and the percentage of pregnant patients who judged blood loss to be much more than a normal menstruation was low

Table 6. Percentage of patients with gastrointestinal side-effects and analgesic injections

		Vomiting	Diarrhoea	Analgesic injection
Pregnant	Vacuum aspiration (n=216)	1·9	0·0	0·5
	Prostaglandin therapy (n=203)	29·6	21·2	12·3
Non-pregnant	Vacuum aspiration (n=29)	0·0	0·0	0·0
	Prostaglandin therapy (n=25)	28·0	28·0	8·0

(6·2% for prostaglandin treatment compared with 1·4% for vacuum aspiration). Since the analgesic treatment was not the same in the two treatment groups it is impossible to assess which therapy is the more painful. It is obvious, however, that the prostaglandin treated patients experienced more pain. The frequency of clinically suspected pelvic infection was higher after prostaglandin therapy (3·5%) than after vacuum aspiration (1·6%) but the difference was not significant. A low frequency of pelvic infection in spite of prolonged bleeding was also reported in the previous WHO multicentre study in which vaginal 16,16-dimethyl-PGE_1 was used (WHO 1982).

Since a delay of menstruation, but not a positive pregnancy test, was the determining criterion for inclusion in the study, 54 non-pregnant patients were also treated. If a non-surgical procedure is to be used on a larger scale for menstrual induction, it is conceivable that a pregnancy test will not always be performed prior to treatment because of e.g. economic reasons. It is, therefore, important that the results of the present study indicate that the clinical events were similar in both pregnant and non-pregnant patients for both treatments.

The development of a non-surgical method for termination of early pregnancy which is safe and effective is an important objective from health, demographic and policy perspectives. The present study shows that prostaglandin therapy can be as effective as vacuum aspiration but the frequency of gastrointestinal side-effects is higher. A previous acceptability study indicated, however, that despite the higher frequency of side-effects a majority of patients remained very positive to prostaglandin treatment after abortion (Rosén *et al.* 1984). The recent finding that a combination therapy of anti-progestin and prostaglandin has a low frequency of side-effects (Bygdeman & Swahn 1985), is likely to make the non-surgical alternative even more acceptable to patients.

Acknowledgment

The prostaglandin analogue, 16-phenoxy-tetranor-PGE_2 methyl sulfonylamide was kindly provided by Schering AG, Berlin.

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Received 3 November 1986
Accepted 28 January 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol. 94, pp. 957–962

Is centralized hospital care necessary for all insulin-dependent pregnant diabetics?

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Summary. A retrospective population study in Northern Ireland examined the benefits of centralized care in insulin-dependent diabetic pregnancies. In the 5 years 1979–1983, there were 139 250 deliveries in Northern Ireland and of these 221 pregnancies occurred in 187 insulin-dependent diabetic patients; 100 were managed entirely in peripheral maternity units, 61 were referred from a peripheral unit to the Royal Maternity Hospital, Belfast and 60 were managed entirely in this central referral hospital. The patients referred from the periphery had the worst past obstetric history with a combined perinatal mortality rate of 200 per 1000. During the study period the perinatal mortality rate was 107 for the referred pregnancies, 33 for those managed entirely in the peripheral units and 18 for those managed at the Royal Maternity Hospital. If those pregnancies terminated for fetal abnormality, and deaths beyond the perinatal period are included, the figures for total fetal loss were 15·5%, 5·5% and 7·1% respectively. Overall the major congenital malformation rate was 7·5%, and for the respective groups 6·5%, 3·0% and 13·0%. For the general population during the same period the perinatal mortality rate was 1·4% and the major congenital malformation rate was 2·5%. Thus it is suggested that only peripheral hospitals which can offer combined antenatal/endocrine care and with a neonatal intensive care unit should undertake the management of the pregnant diabetic.

Pregnancy in insulin-dependent diabetics is still associated with considerable perinatal morbidity, and a perinatal mortality rate approximately three times that for non-diabetic pregnancy (Beard & Lowy 1982; Persson *et al.* 1983; Traub *et al.* 1983; Molsted-Pedersen 1980). Nevertheless, a distinct improvement has taken place in recent years which has kept pace with that for the general population. Whether or not this improvement is representative of the country as a whole is not clear, as virtually all published data come from large referral centres where a relatively uniform programme of management is provided by a team of physicians, obstetricians and neonatologists, and where intensive care facilities for the infant are available. The recent United Kingdom survey of

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the outcome of pregnancy in insulin-dependent diabetic mothers suggested that those centres dealing with the smallest number of patients per year had the highest perinatal mortality rates (Persson *et al.* 1983). This survey relied on the relatively uncertain technique of postal questionnaire and replies were not received from the obstetricians in some hospitals. A population-based study in Washington State, USA (Connell *et al.* 1985) obtained information by personal visit and enquiry but unfortunately some hospitals refused to participate Thus the widely stated need for centralization of care for the pregnant insulin-dependent diabetic has yet to be confirmed conclusively because reliable information from hospitals other than the major teaching centres is not readily available.

The aim of the present study was to document the outcome of all pregnancies in insulin-dependent diabetic mothers in all the obstetric units in a single area. Northern Ireland has a population of 1·6 million and is served by 17 obstetric units, four of which are in Belfast. Five of the units serve as regional referral centres, but the major referral centre for diabetic women is the Royal Maternity Hospital in Belfast, where there has been a combined metabolic/antenatal clinic for more than 30 years. There is a high level of communication and co-operation throughout the country between both the obstetricians and physicians caring for patients with diabetes, thus greatly facilitating the study. Also, by analysing the data with reference to those patients who attended the peripheral hospitals and those who were referred from these hospitals to the major regional centre, the value of centralization of care for the pregnant diabetic may be clarified.

Patients and methods

Data were collected from all known pregnancies in insulin-dependent diabetic women for the 5-year period 1979–1983 during which time the total number of deliveries was 139 250 throughout Northern Ireland. Patients who were treated with insulin during the pregnancy but discontinued it after delivery were excluded from the study. In this group the outcome of pregnancy is better than for insulin-dependent diabetics (Molsted-Pedersen 1983) so the inclusion of such patients would favourably influence the results.

To ensure that all pregnancies were documented, a variety of methods was used to trace and cross-reference the names and hospital numbers. No single register proved to be accurate, with many diabetics missing and several non-diabetic patients being included—even on lists evolved from the birth register.

Other sources of data that were used included admission summaries in the labour wards and special care nurseries, personal recollection by obstetricians and physicians, labour ward records, congenital abnormality records, diabetic clinic and medical outpatient records. All the data were collected by a personal visit by one of the authors to each of the hospitals to examine patients' records and extract the information directly for subsequent computer storage. Only 4 of the 17 obstetric units managed no diabetic mothers during this time: in the remainder the number per year ranged from less than 1 up to 40 in the Royal Maternity Hospital.

A total of 221 pregnancies were identified in 187 patients, 121 were managed in the Royal Maternity Hospital, Belfast and the remaining 100 pregnancies in 12 other obstetric units. The patients in the Royal Maternity Hospital group were further subdivided into those who attended the combined diabetic/antenatal clinic at that hospital from the onset of pregnancy, and those who had been referred from other centres, their initial antenatal and diabetic care having been undertaken in the local hospital. The number of pregnancies per year in diabetics in Northern Ireland increased from 36 in 1979 to 67 in 1983; the percentage of those delivered in the major centre remaining relatively static at approximately 55%. The three groups had similar age distribution (Table 1), but those patients attending the Royal Maternity Hospital throughout had the longest mean duration of diabetes, 13·6 years, and the highest incidence of vascular complications, 12·5% (mostly retinopathy and nephropathy). The patients referred to the Royal Maternity Hospital from peripheral hospitals had by far the worst past obstetric record, with a combined perinatal mortality rate of 200/1000 in their previous pregnancies.

Patients attending the Royal Maternity Hospital throughout tended to book early, at a mean gestation of 11 weeks compared with 14 weeks in other hospitals. To assess diabetic control in early pregnancy the blood sugar level at booking, as recorded in the antenatal chart or the diabetic chart at the time of pregnancy diagnosis, was used. As these values were a mixture of random samples, timed samples and patients'

Table 1. Characteristics of insulin-dependent patients managed in three ways

Variable	Royal Maternity Hospital	Referred to Royal Maternity Hospital during pregnancy	Other consultant obstetric units
No. of patients	56	51	80
No of pregnancies	60	61	100
Mean age (years)	27·5	26·0	26·7
Mean duration of diabetes (years)	13·6	9·5	10 2
Vascular complications (%)	12·5	8·0	7 0
Previous perinatal mortality (%)	5·0	20·0	12·0

glucometer readings, the exact usefulness may be questioned, but they did show that only 36% of the Royal Maternity Hospital patients had satisfactory control (blood glucose <7mmol/l) at this early stage: the corresponding percentage for those delivered in the peripheral hospitals was 29% and for those patients who were referred it was only 10%. Overall 33% of patients had isolated blood glucose levels at this stage of >10 mmol/l. Those patients attending the Royal Maternity Hospital had HbA1 estimated and only 12 of the 60 pregnancies had a level in normal range (<7·5 mmol/l) and 12 had levels >10 mmol/l, supporting the indication from the blood sugar levels that most of them had poor diabetic control in early pregnancy.

The mean gestational age at delivery for all patients was 36·6 weeks and the mean birthweight was 3368 g; there was no difference between the three groups. The incidence of a birthweight >95th centile was low at 3·3%. The caesarean section rate in the peripheral hospitals was highest at 61%, for those referred to the Royal Maternity Hospital, it was 52% and for those attending there throughout, 44%. The caesarean section rate for the Northern Ireland population during the study period in the peripheral hospitals was 8% and in the Royal Maternity Hospital, 15%.

The outcome of the 221 pregnancies, including four sets of twins, is shown in Table 2. The miscarriage rate was 7·7% overall and did not differ between the groups. Four pregnancies were terminated, in each case the indication was a lethal fetal abnormality demonstrated with ultrasound scanning; three fetuses were anencephalic and one had renal agenesis. There were eight stillbirths and two first week deaths, a perinatal mortality rate of 50; the rate for the general population was 14 over the same period When divided into the three groups, the referred patients had the highest stillbirth rate—10·7% (general population 0·8%), but no neonatal deaths. In contrast, the low perinatal mortality rate of 18·5 in the Royal Maternity Hospital group was a result of no stillbirths and only one first-week death. For those patients managed in the peripheral units the perinatal mortality rate was 33, two stillbirths and one first-week death In total, four further babies died after the age of 7 days, two before 28 days and two between 1 and 3 months of age.

Table 2. The overall outcome of pregnancy in insulin-dependent diabetics in Northern Ireland, 1979–1983

Variable	Royal Maternity Hospital	Referred to Royal Maternity Hospital during pregnancy	Other consultant obstetric units
Pregnancies (*n*)	60	61	100
Miscarriage (*n*)	4	3	10
Abortion (*n*)	2	2	0
Stillbirth (*n*)	0	6	2
Livebirth	54	50	88
Early neonatal death	1	0	1
Late neonatal death	1	0	1
Infant death	0	1	1
Perinatal mortality (rate/1000 births)	18 5	107	33·3
Total fetal loss*	7·1%	15·5%	5·5%

* Includes abortions, stillbirths and deaths within 1 year of life.

There were 15 major fetal malformations, including those four where the pregnancy was terminated. Eight occurred in the Royal Maternity Hospital group, four in the referred group and three in the peripheral hospitals. These comprised neural tube, renal and cardiac defects (Table 3). The overall major malformation rate for the series was 6·8% compared with the incidence of major congenital malformation in Northern Ireland, which at 2·5% is already one of the highest in the world. Eight lethal abnormalities accounted for 44% of the total fetal loss and included two babies who survived beyond the first week, one for 8 and the other for 80 days. The morbidity for the survivors with major lesions has not been quantified but was considerable, for example one baby had three major operations, two orthopaedic and a nephrectomy, before the end of the first year of his life

Discussion

Most published studies of the outcome of diabetic pregnancies have come either from large centres (Traub *et al.* 1983; Molsted-Pedersen & Kuhl 1986; Jervell *et al.* 1980) where the data are readily available, or have been more general surveys and relied upon single sources for their data such as birth registers in the Norwegian study (Jervell *et al.* 1980) or replies to a postal survey in the United Kingdom (Beard & Lowy 1982). In the present study no single register of births to diabetic mothers proved accurate: in all lists non-diabetics were included and many insulin-dependent diabetics were omitted in error. A final list of patients was obtained by cross-referencing and pooling data from many sources. At the time of the introduction of U100 insulin to Northern Ireland in 1984, an attempt was made to place all insulin-dependent diabetics attending hospital clinics in Northern Ireland on a register, and this was one of the most helpful data banks. It is disappointing that current record systems seem to be so inadequate in view of the clerical time and effort expended upon them. Computerization of hospital records may improve the situation.

The overall prevalence of diabetic pregnancies (excluding gestational and non-insulin-dependent diabetes) during this study was approximately 1 in 700. This figure is similar to that for the Republic of Ireland (Drury 1986), Denmark (Pedersen 1977), and within the estimated range for the USA (Connell *et al.* 1985).

The number of pregnancies in the three groups of patients doubled over the 5 years of the study, a trend also noted in Sweden, and perhaps reflecting an actual increase in the prevalence of insulin-dependent diabetes, as recorded in Denmark (Green *et al.* 1981) and Poland (Rewers *et al.* 1985). Alternatively, more diabetic women may now be prepared to embark on pregnancy as they recognize that it is safer for them to do so and that the outcome is in general a happy one. Indeed, in the Royal Maternity Hospital this upward trend in the number of pregnant diabetics has continued for the 2 years following the study period. The proportion of insulin-dependent diabetic patients from Northern Ireland attending the Royal Maternity Hospital throughout pregnancy each year did not alter significantly over the 5 years. This contrasts with Scandinavia where the major centres are managing an increasing proportion of the total number of diabetic pregnancies (Molsted-Pedersen & Kuhl 1986; Drury 1986).

The patients in the Royal Maternity Hospital group had a higher incidence of the complications of diabetes, possibly attributable to their higher mean age, or to more assiduous ophthalmological examination at the diabetic eye clinic at the Royal Victoria Hospital. As this hospital is the main teaching unit in Northern Ireland, it tends to attract those diabetic patients who have more severe complications or who cannot be managed in their local hospital.

Table 3. Distribution of congenital malformations occurring in diabetic pregnancy in Northern Ireland, 1979–1983

	Royal Maternity Hospital ($n = 60$)	Referred to Royal Maternity Hospital during pregnancy ($n = 61$)	Other consultant obstetric units ($n = 100$)
Major			
Fatal	4	3	1
Non-fatal	4	1	2
Minor	2	0	2
Major malformation rate (%)	13	6·5	3

The recorded miscarriage rate of 7·7% is less than the generally accepted incidence for the non-diabetic population. This would seem to contradict the widely held belief that miscarriage is more common in diabetic pregnancies, although in most large series the miscarriage rate is not reported. The information relating to early miscarriage is the least accurate data in this report, as in some hospitals there was no consistent way of checking admissions of diabetics to gynaecology wards.

Major congenital malformations were responsible for approximately 50% of the total fetal loss—this compares with 43% in Washington State, USA (Connell *et al.* 1985) and 60% in Copenhagen (Molsted-Pedersen & Kuhl 1986), (in this latter series several pregnancies in patients judged to be at risk were terminated, thus potentially lowering the reported abnormality rate).

Since it became clear that diabetic patients with high levels of HbA1 in early pregnancy are at the greatest risk of producing an abnormal fetus (Miller *et al.* 1981; Leslie *et al.* 1978) it has been shown (Fuhrmann *et al.* 1983; Steele *et al.* 1982) that prepregnancy counselling and lowering of preconceptional blood glucose levels will reduce the incidence of congenital malformation This was not the case in the Royal Maternity Hospital group where 70% of patients had received some form of counselling (compared with no such documented counselling in the peripheral hospitals) but there was no improvement in outcome. The mean blood glucose at booking in these patients was only marginally better than in other groups and the HbA1 level showed that in only 20% had the counselling resulted in satisfactory control in or around the time of conception. These patients had more severe underlying disease, and it may be that factors other than blood glucose levels are of importance in relation to fetal malformation.

In the peripheral hospitals three out of seven deaths were associated with fetal cardiomyopathy. This is not a congenital malformation but is associated with elevated maternal blood glucose levels in later pregnancy (Halliday 1981). There were no similar cases in the Royal Maternity Hospital group where all patients self-monitored their capillary blood glucose level four times daily, usually with a reflectance meter. This supports the value of intensive monitoring and good blood glucose control in the third trimester: in the peripheral hospitals the majority of patients relied only on urine testing.

The overall perinatal mortality rate of 50, three times that of the general population, was anticipated at the outset of the study and is in keeping with that of other recent large studies. More notable is the perinatal mortality rate of 18 in those diabetic patients managed at the Royal Maternity Hospital from first booking, a rate only marginally higher than that for the whole population during the period of the study. This compares with the very high perinatal mortality rate of 107 in those patients who were transferred later in pregnancy to the Royal Maternity Hospital from another unit where they had been attending for antenatal care The difference between these groups is highly significant and almost entirely attributable to the occurrence of six intrauterine deaths in the referred patients. Indeed the incidence of stillbirths in this group was more than ten times that of the general hospital population. In all cases the diabetic control was unsatisfactory but only one of these babies had a lethal abnormality. This serves to emphasize that the use of cardiotocography and serial ultrasound to assess fetal well-being is of limited value in diabetic pregnancy Fetal death in these circumstances is unpredictable probably because the cause of death is metabolic in origin. In many series of diabetic pregnancy (Steele *et al* 1982) sudden intrauterine death has followed a normal cardiotocograph and it seems that the single most important way to prevent deaths in the third trimester is by strict control of maternal blood glucose levels.

It has become recognized that the value of perinatal mortality rates as a method of obstetric audit is very limited: advances in neonatology have meant the postponement of many perinatal deaths into the late neonatal period. For this survey, to achieve a more realistic appraisal of outcome these deaths have been included in the estimation of total fetal loss (Table 2). It is clear that the outcome among those patients who were transferred remained significantly worse than in the other two groups. Thus the thesis that 'centralized care' is necessary for all pregnant diabetic patients is supported by this difference in the intrauterine death rate between the two groups and by the observation that blood sugar control was poor in cases from the peripheral hospitals Equally, the fact that the outcome among cases transferred was so poor may be used to support the suggestion that the patients most at risk were identified correctly and transferred. However, it may be more realistic to suggest that had these patients been transferred much earlier in their pregnancy then the outcome may have been much better.

Similarly, the very low perinatal mortality rate of 33 in the diabetics delivered in the peripheral units was partly a result of transferring the patients most at risk. This rate is of the same order as that obtained in some major centres during this period and does not support findings of two other community surveys (Beard & Lowy 1982; Connell *et al* 1985) that the outcome of pregnancy in insulin-dependent diabetics is significantly worse in those units delivering the fewest diabetics per year, although neither survey was confined to a small region well integrated from an obstetric and diabetic care aspect.

In conclusion this study has demonstrated that when pregnant diabetic patients are managed throughout their pregnancy in a regional hospital which offers a combined approach by physicians, obstetricians and neonatologists it is possible to reduce the perinatal mortality rate almost to that of the general population. In contrast the poor outcome among patients requiring transfer from a peripheral unit suggests that the referral of problem patients is often too late. Thus if patients are to be managed in centres outside the regional unit then not only must they be selected very carefully but ideally only peripheral units with a well motivated obstetrician and physician, and neonatal care facilities should be involved.

Acknowledgments

The authors thank all those physicians and obstetricians in Northern Ireland who kindly gave consent for us to study the hospital records of their patients. Thanks are also due to Professor N C. Nevin for the use of his computer facilities, Mr T. J. McGurk for help in analysing the results and Miss Karen Dickson for preparing the manuscript.

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Received 11 August 1986
Accepted 3 February 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol. 94, pp 963–966

The continuous measurement of transcutaneous carbon dioxide tension (TcPCO_2), an atraumatic tool to verify fetal acidosis?

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Summary. TcPCO_2 monitoring of the fetus during labour was evaluated as an atraumatic tool to identify or exclude fetal acidosis in 224 high-risk deliveries. A heated electrochemical sensor with a measuring temperature of 39 °C ($n = 105$) or 44 °C ($n = 119$) was applied to the fetal scalp. There was a statistically significant correlation between the TcPCO_2 and the fetal blood pH at both temperatures. The sensitivity of the method was 0·90 and 0·61 at the two measuring temperatures of 44° or 39° respectively and the specificity was 0·93 and 0·79 respectively. The negative predictive value was high (0·99 and 0·95 respectively), but the respective positive predictive values were only 0·53 and 0·24. We conclude that the continuous measurement of the TcPCO_2 is a valid additional tool to exclude fetal acidosis in most cases where fetal distress is indicated by the heart rate pattern but a TcPCO_2 value above the cut-off point should be verified by an additional method to avoid unnecessary operative deliveries.

The pH measurement of fetal blood is one basis of modern supervision of the unborn child (Saling 1985). The physiological range of the pH values was defined by means of intermittent fetal blood sampling according to the technique first described by Saling (1961). It has been possible to define prepathological and pathological values for the fetus during labour (Grimwade 1970), and to a large extent it is possible to exclude fetal distress when values are within the normal range (Beard *et al.* 1967). An early detection of falling pH values is essential to give the obstetrician a chance for prophylactic action either by intrauterine resuscitation or operative delivery. Thus it is desirable for fetal surveillance to detect preacidotic values (pH 7·20–7·24) to avoid particularly severe acidosis at the moment of delivery. While fetal blood analysis (FBA) was an important step forward in providing an assessment of the fetus during labour it has the disadvantage of being a single point test and, therefore, often has to be repeated at short intervals; thus a continuous record of a biochemical indicator is preferable (Saling 1984). To investigate the efficacy of the transcutaneous measurement of carbon dioxide partial pressure (TcPCO_2) in the fetus during labour in predicting a critical rise in fetal acidosis we performed a clinical trial using the newly available Severinghaus electrode.

Subjects and methods

The Severinghaus electrode includes a glass pH electrode, a reference electrode and a heating element. PCO_2 is calculated by means of a microprocessor from the pH changes caused

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when CO_2 diffuses from the skin into the measuring chamber (Severinghaus *et al.* 1978).

During the course of this study TcPCO_2 measurements were performed on 224 fetuses. The mean duration of the recording was 3 h and 4 min (range 22 min–9 h and 16 min). This method was used in all patients in addition to continuous cardiotocography (CTG) combined with intermittent fetal blood analysis. The patients included in the study had suspicious, prepathological or pathological fetal heart rate (FHR) patterns according to the Hammacher score on the admission CTG and/or on the CTG during the subsequent labour ward tracing before the application of the TcPCO_2-electrode (Hammacher *et al.* 1974). FBA was performed on 262 occasions to verify fetal distress when the following CTG changes were observed: decelerations—variable, late, early (the latter if FHR decreased by >60 beats/min)—for more than 10 min or three contractions, it was performed immediately in the presence of severe bradycardia (<100 beats/min) Of the 224 women, 154 were para 0, 31 were para 1 and 39 were para 2 or more. Of the 224 infants, 122 were born spontaneously, 54 by vacuum extraction, 15 by modified outlet forceps and 33 by caesarean section. The indications for operative delivery were arrest of labour in 72; critical pH levels (<7·25 confirmed by subsequent FBA) in 21; and a pathological FHR pattern after the fetal head had reached the pelvic floor in the other nine. All the infants were vertex presentations and they were all vigorous at birth (modified Apgar score ≥7) (Saling & Wulf 1971) The umbilical artery pH was ≥7·20 in 211 infants, 7·09 in one and between 7·10 and 7·19 in 12 infants Epidural analgesia was used in 102 patients. All the patients gave consent to the TcPCO_2 measurement after detailed explanation.

A modified Severinghaus electrode was used for all the measurements (Severinghaus *et al.* 1978). By modification of a commercially available TcPCO_2 electrode (Radiometer E 5230), we have succeeded in improving the application to the fetal head and also integrated an ECG electrode into the measuring chamber of the transcutaneous system, so that penetration of the fetal scalp is no longer necessary Details of this design are reported elsewhere (Schmidt *et al.* 1982). The measurement was performed at a temperature of 39 °C in 105 patients and at 44 °C in the other 119. The drift of the electrode during the study was <2% in most cases, the maximum drift being 8%. As the optimal measuring temperature is still controversial, the sensor was alternatively heated at 39 °C or 44 °C in consecutive patients who fulfilled the criteria for inclusion in the study. In 22 patients the attempt to apply the electrode was not successful because the electrode became dislodged from the fetal head after fixation.

Statistical methods

The TcPCO_2 measurements, the biochemical results and the clinical data of the patients were evaluated with the Statistical Package for Social Science (SPSS) of Northwestern University. For the comparison between the TcPCO_2 and the pH level the linear correlation coefficient, the slope and the intercept were calculated. An 'action line' for the TcPCO_2 measurement in the clinical routine was defined retrospectively. The cut-off point was established from the fact that below this limit no acidosis (pH <7·20) had been observed during the study (Saling & Wulf 1971). The efficacy of the TcPCO_2 to identify or exclude a risk to the fetus was evaluated by calculating the sensitivity and specificity as well as the predictive value (Grant 1982). This was investigated using an arbitrary action line at both pre-chosen temperatures corresponding to the value of 55 mmHg for the PCO_2 after correction to the blood gas level (Severinghaus 1981). The sensitivity and specificity as well as the predictive value of the procedure to recognize or exclude a fetal blood pH value of <7·25 was calculated.

Results

Comparison of the fetal blood pH value with the synchronously recorded TcPCO_2 measured at 39 °C showed a correlation coefficient of −0·57, an intercept of 812·09, a slope of −1·03 (P<0·001). No acidosis occurred with a TcPCO_2 of ≤63 mmHg (8·4 kPa) and no critical fall of the fetal pH (<7·25) was observed with a TcPCO_2 of ≤55 mmHg (7·28 kPa) (Fig. 1).

From the data obtained at 44 °C, we calculated a correlation coefficient of −0·53, a slope of −0·99 and an intercept of 788 83. No acidosis occurred below a value of 80 mmHg (10·67 kPa), and preacidosis could be excluded when the TcPCO_2 values were <70 mmHg (9·33 kPa) (Fig. 2). The correlation coefficients at the two temperatures were not significantly

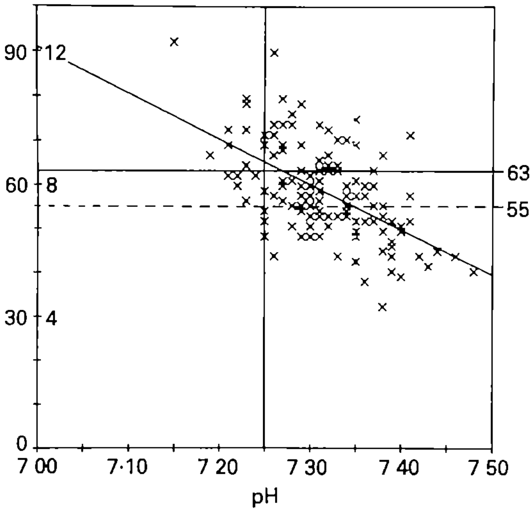

Fig. 1. Comparison of values of the transcutaneously measured carbon dioxide partial pressure (TcPCO$_2$) and the pH value measured in fetal blood (FBA) during measurements at 39 °C $n = 135$; $r = -0{\cdot}57$ TcPCO$_2$ = $-1{\cdot}03\times$pH (FBA)+812·09. $P<0{\cdot}001$

different ($P>0{\cdot}05$). The TcPCO$_2$ measurements at 39 °C correctly excluded preacidosis in 96 fetuses and correctly identified the condition in eight. In five fetuses preacidosis was not recognized (the pH level was >7·20 in all fetuses). In 26 fetuses preacidosis could not be excluded; the TcPCO$_2$ level exceeded the value of the action line, whereas the pH was >7·24.

The TcPCO$_2$ measurements at 44 °C identified preacidosis correctly in nine fetuses. In one fetus preacidosis was not recognized (the pH was >7·20), and in eight cases it could not be excluded. The results detailed in Table 1 show a sensitivity of 0·61 and a specificity of 0·79 at 39 °C, whereas at 44 °C the sensitivity was 0·90 and the specificity was 0·93. At 39 °C and 44 °C, respectively, the positive predictive values were 0·24 and 0·53, and the negative predictive values were 0·95 and 0·99.

Discussion

Measuring the pH in the fetal blood is still a well established technique to assess the status of the unborn infant. Part of its reliability is due to the fact that by measuring the pH, both the respiratory disturbance (rise of PCO$_2$) and a rise in metabolic acidity are detected (Saling 1984). A large number of clinical trials have been reported which attempt a continuous recording of the tissue pH (Young *et al.* 1978).

As the transcutaneous measurement avoids trauma to the skin and still provides continuous information it has obvious attractions for the supervision of the fetus during labour. We have observed a complication in only one patient where a 2nd degree skin burn occurred after a 3-h measuring period at 44 °C.

Unlike TcPO$_2$ measurements, the TcPCO$_2$ values provide a reliable measure of the PCO$_2$ in fetal blood even when obtained from the fetal scalp during labour (Hansen *et al.* 1984, Schmidt *et al.* 1982). Due to the CO$_2$ production of the tissue and the effect of the raised temperature, the TcPCO$_2$ values exceed those in the fetal blood. This effect, which is proportional to the prechosen measuring temperature, should not be misinterpreted as a lack of accuracy in measuring the PCO$_2$ of the blood and can be corrected by a formula proposed by Severinghaus (1981).

When using TcPCO$_2$ for the prediction of fetal acidosis one must remember that with this technique only one of the factors that cause the acidity in the fetal blood is measured (Saling 1984). In spite of this, a clinically relevant complication should be indicated by an increase of the TcPCO$_2$ level for three reasons: first, feto-maternal transfer of CO$_2$ may be impaired, second, a certain amount of CO$_2$ might be displaced by an increase of lactic acid in the fetal blood (Saling 1984); and third, a rise in TcPCO$_2$ may occur due to an increase in the difference between TcPCO$_2$ value and the fetal blood

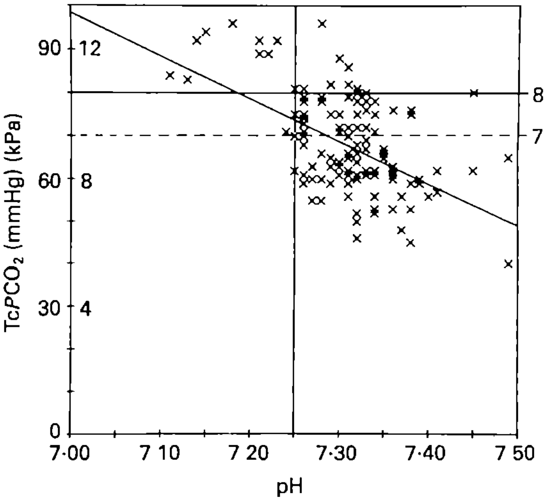

Fig. 2. Comparison of values of the transcutaneously measured PCO$_2$ and the pH value of the FBA during measurement at 44 °C $n = 127$, $r = -0{\cdot}53$. TcPCO$_2$ = $-0{\cdot}99\times$pH (FBA)+788·83

Table 1. Potential of the TcPCO_2 to exclude and identify a pH of <7·25 in the fetus during labour at a measuring temperature of 44 °C and 39 °C

	39 °C	44 °C
Specificity	0 79	0·93
Sensitivity	0·61	0·90
Predictive value (+)	0·24	0 53
Predictive value (−)	0 95	0·99

PCO_2 value during a centralization of the circulation. In this way the transcutaneous measurement could indicate fetal distress even before a disturbance affected blood gas levels. This phenomenon has already been postulated for TcPO_2 measurements in the fetus (Jensen & Kunzel 1980).

While the correlation between the TcPCO_2 and the pH of the fetal blood was not different at the two temperatures chosen, it is obvious from the sensitivity and specificity that the potential clinical benefit is much larger when the sensor is heated to 44 °C. The superior specificity is of special interest when the clinical goal of the technique is a reduction in unnecessary operative deliveries, and a reduction in the number of fetal blood analyses. The TcPCO_2 level in most cases was below the cut-off point when a FBA was indicated from the FHR pattern, so that fetal distress suggested by the CTG-tracing can usually be excluded.

During our clinical trial the occurrence of an acute complication was indicated in all cases by a rise in the TcPCO_2 level to a value above the cut-off point. On the other hand a TcPCO_2 level above the cut-off is not a particularly good predictor of pH below the cut-off as shown by the relatively poor positive predictive value even at 44 °C. Analysis of our fetal TcPCO_2 measurements show that such erroneously high TcPCO_2 values may be caused by the development of a caput succedaneum and by compression of the sensor between the fetal head and the pelvic wall during the progress of labour (Schmidt *et al.*, unpublished observations). In conclusion, continuous, atraumatic TcPCO_2 monitoring seems to be a clinically useful way to improve fetal surveillance especially in high risk labours.

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Received 27 May 1986
Accepted 6 January 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp 967–974

Combined echocardiographic and Doppler assessment of fetal congenital atrioventricular block

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Summary. Fetal heart rate monitoring was combined with fetal echocardiography for examination of atrial reactivity during labour in five fetuses with second or third degree heart block. Alterations in vagal tone accompanying uterine contraction influence atrial rate, even when the ventricle is not under atrial 'control'. Fetal echocardiography enabled diagnosis of the underlying basis of the arrhythmia and located the optimal position for recording atrial activity with an external heart rate monitor. External and internal monitoring of atrial activity demonstrated reactivity during labour. Two patients were delivered vaginally after monitoring throughout labour. One mother preferred elective caesarean delivery. Caesarean section was required in another for cephalopelvic disproportion and in the remaining woman for late decelerations. These monitoring techniques provide an assessment of fetal well-being in the presence of fetal bradycardia due to variable degrees of heart block.

For more than 100 years obstetricians have recognized that intrapartum slowing of the fetal heart may be a sinister sign.

During the past two decades the monitoring of fetal heart rate and heart rate variability has become an important component in the assessment of the fetus in late pregnancy and labour (Hon & Quilligan 1967; Parer 1983). More recently, interest and understanding of the structure and function of the developing human fetal heart have increased, with echocardiographic imaging techniques for the examination of the heart of the second and third trimester fetus (Kleinman & Santulli 1983; Allan *et al.* 1981). M-mode and pulsed Doppler echocardiography has permitted detailed analysis of disturbances in fetal cardiac rhythm (Kleinman *et al* 1983; Allan *et al.* 1983). These techniques, by allowing analysis of hard-copy recordings of cardiac motion against time, may allow perturbations in the atrioventricular contraction sequence to be analysed. These conduction defects are not easily assessed with external monitoring devices (continuous wave Doppler heart monitors or transabdominal electrocardiographic equipment) as these do not provide information about fetal atrial activity.

We have investigated five patients with sustained bradycardia secondary to varying degrees of atrioventricular block. Using a combination of continuous wave Doppler external heart rate monitoring equipment, as well as M-mode and pulsed Doppler echocardiographic equipment for the assessment of atrioventricular contraction sequence and heart rate alterations during active labour, we were able to demon-

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strate normal atrial rate changes. We believe that these experiences demonstrate the utility of these combined techniques for safe monitoring of such fetuses. They may, in some cases, enable the medical team to avoid needless caesarean delivery.

Subjects and methods

Fetal echocardiographic assessment of two-dimensional cardiac anatomy was performed using standard tomographic imaging techniques as described previously (Kleinman & Santulli 1983), and using either a Hewlett-Packard 77020A phased array ultrasonograph (Hewlett-Packard Corp., Andover, Massachusetts, USA) or an Advanced Technology Laboratories (ATL) MK-600 mechanical scanning device (Advanced Technology Laboratories, Bellevue, Washington, USA) with 5·0, 3·5 or 3·0 MHz transducers. Pulsed Doppler assessment of transatrioventricular valve and great arterial flow-velocity waveforms was accomplished using the ATL MK-600 imager. Real-time-directed M-mode studies of atrioventricular contraction sequence were performed using both echocardiographic devices. Simultaneous M-mode information from fetal ventricles and atria were recorded using the Hewlett-Packard phased array scanner's dual M-mode capabilities. The M-mode scans were recorded in hard copy at 50 mm/s using a strip chart recorder. External fetal heart rate monitoring was performed using a Litton FM660 (AMS Corp., Hamden, Connecticut, USA) continuous wave Doppler instrument.

Results

Patient no. 1

A 34-year-old primigravida was studied at 37 weeks gestation because of sustained fetal bradycardia of 45 beats/min. She had been well during the pregnancy except for a painful and swollen ankle that was attributed to a 'sprain' despite a lack of a history of trauma. There was no evidence of polyhydramnios. Maternal anti-nuclear antibody (ANA) was strongly positive. Fetal echocardiographic study demonstrated a structurally normal, albeit dilated, heart with an atrial rate of 115–125 beats/min and a ventricular rate of 45 beats/min (Fig. 1) without a fixed relation between atrial and ventricular activity. A diagnosis of complete heart block, secondary to maternal systemic lupus erythematosus, was established. During the next 24 h labour was induced with intravenous oxytocin. Echocardiographic monitoring of atrial rate during active labour demonstrated normal heart rate variability throughout In addition, despite continued evidence of complete atrioventricular block, external heart rate monitoring demonstrated a normal pattern of heart rate variability around the baseline ventricular rate of approximately 75 beats/min. The fetus tolerated labour and vaginal delivery well and the healthy 3200 g male infant was found to have complete atrioventricular block at birth, with a narrow-QRS-complex ventricular rate of 90 beats/min (Fig. 2). Echocardiography demonstrated an enlarged but otherwise structurally normal heart. There was no evidence of congestive heart failure. The child was discharged without requiring pacemaker insertion and has continued to develop normally. The mother has required continued medical care for systemic lupus erythematosus

Patient no. 2

A 24-year-old primigravida was seen at 38 weeks gestation because of irregular fetal bradycardia of 75–80 beats/min. She had received regular antenatal care and, until the day of admission, had been recorded as having a normal fetal heart rate throughout the third trimester. There was no evidence of polyhydramnios. Maternal ANA was negative. Fetal ultrasound showed no fetal oedema. Cardiac anatomy was normal on two-dimensional echocardiographic study. M-mode echocardiography demonstrated 2:1 atrioventricular block with isolated episodes of 1:1 atrioventricular conduction. On the day after admission, labour was induced with oxytocin. During labour normal heart rate changes were documented, with the baseline ventricular rate approximating 80 beats/min. Cephalopelvic disproportion was diagnosed at 6 cm of cervical dilation with onset of maternal fever to 38·9°C. After development of maternal fever, the fetal heart rate increased to 180 beats/min with normal variability The child, a normal male infant weighing 3600 g, was born by caesarean section. The heart rhythm immediately after birth was sinus, at 160 beats/min, with the gradual development of Mobitz Type I (Wenckebach periodicity) second degree atrioventricular

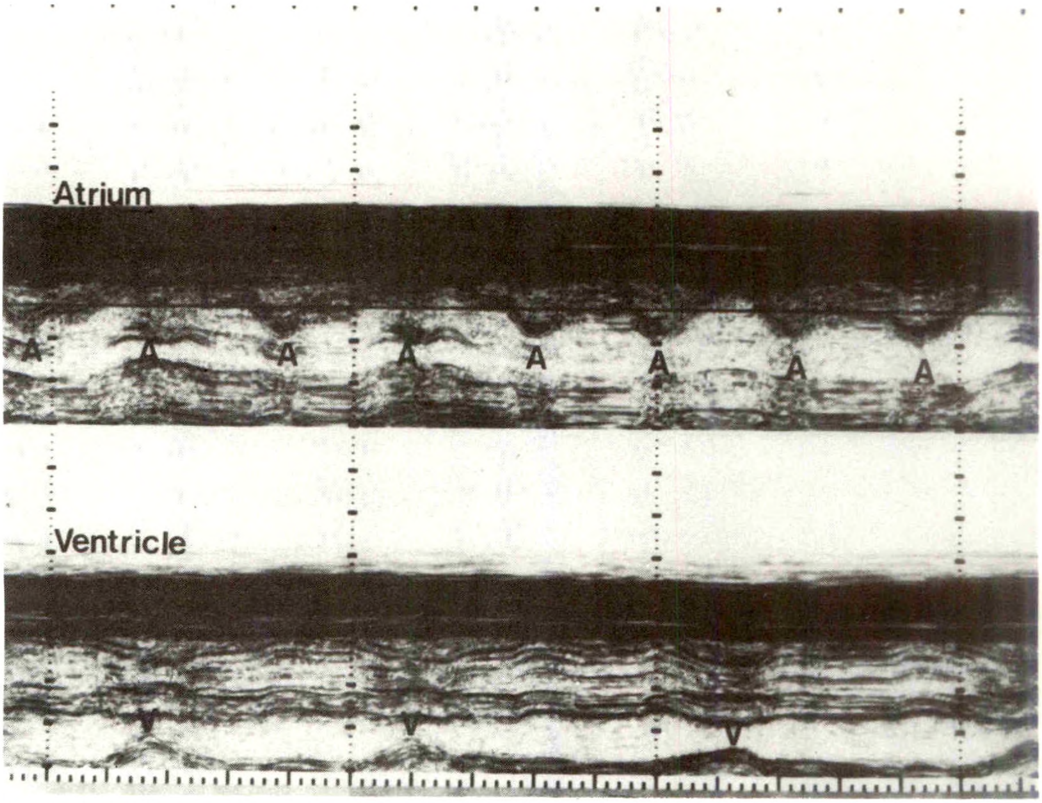

Fig. 1. Dual M-mode echocardiographic tracings from the fetus in patient no. 1. Complete heart block was diagnosed on the basis of atrioventricular dissociation, with atrial wall undulations (A), in the upper tracing, bearing no fixed relation to the ventricular contractions (V), seen on the simultaneously recorded tracing from the ventricular body (lower tracing). The atrial rate varied from 115–125 beats/min, while the ventricular rate was 45–50 beats/min.

block within 5 min of birth; 15 min later the heart rhythm became 2:1 Mobitz Type II second degree atrioventricular block. There was no evidence of congestive heart failure. Before discharge a 24-h Holter monitor of heart rhythm demonstrated Mobitz Type I and Type II atrioventricular block. The baby was discharged in excellent condition. At follow-up 6 weeks later the baby was in complete heart block but was asymptomatic. He remains in good health despite persistent complete heart block.

Patient no. 3

A 38-year-old primigravida was referred at 34 weeks gestation due to a fetal bradycardia of 50–60 beats/min. Maternal medical history was negative. Maternal ANA and anti-Ro titres were highly positive. There was no polyhydramnios. Fetal ultrasound showed normal cardiac anatomy. There was no fetal oedema. Complete heart block was evident, with an atrial rate of 135–140 beats/min and a ventricular rate of 50 beats/min. External fetal heart rate monitoring during term labour showed atrial reactivity (Fig. 3) with a slow, unreactive ventricular rate. When external monitoring suggested late decelerations (Fig. 4) and scalp electrode monitoring proved inadequate to allow estimation of beat-to-beat variability in atrial rate, the infant was born by caesarean section. Cord anti-Ro titres were strongly positive. The neonatal electrocardiogram showed complete heart block, with an effective heart rate of 45 beats/min, with several ventricular premature contractions per minute. The baby weighed 4 kg; an epicardial permanent ventricular pacemaker was inserted on the 5th day of life, and the baby is alive and well at 18 months of age.

Patient no. 4

A 23-year-old primigravida was referred for assessment at 31 weeks gestation, because of

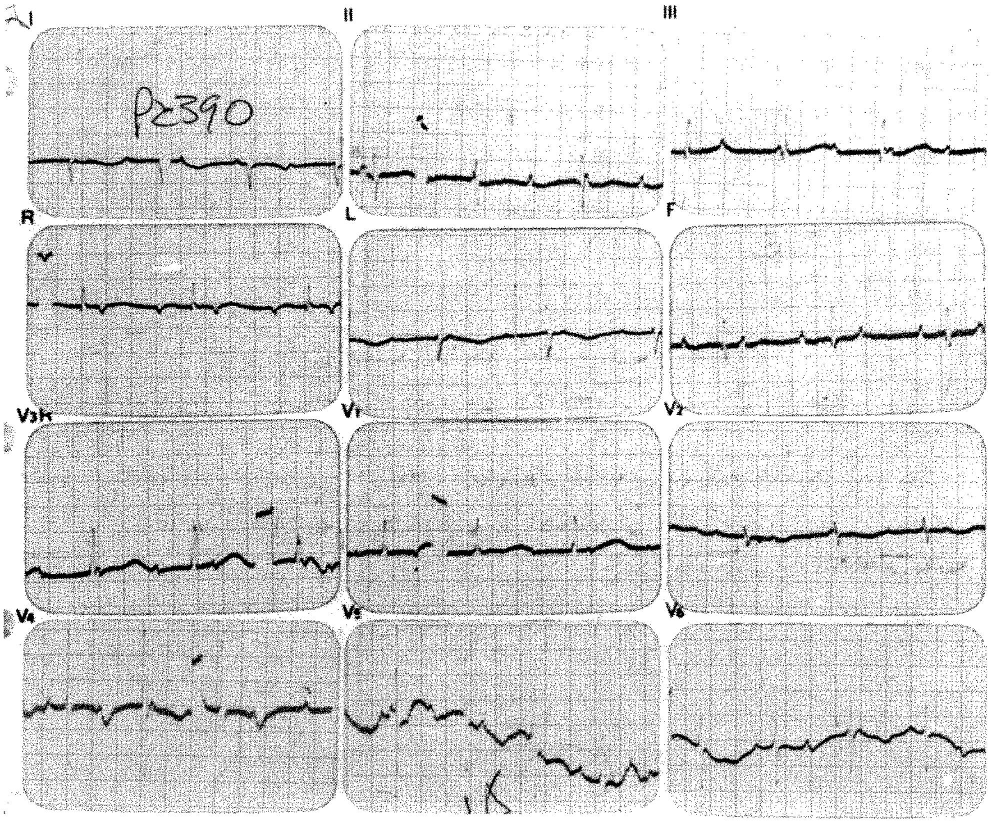

Fig. 2. Twelve-lead electrocardiogram obtained at birth from the infant in patient no. 1. The infant had complete heart block, with an atrial rate of 140 beats/min and a ventricular rate of 70 beats/min.

fetal bradycardia (60 beats/min). Obstetric scanning had demonstrated normal fetal activity, tone, and breathing. The patient was referred for further fetal cardiovascular assessment. The maternal medical history was negative. Maternal ANA and anti-Ro titres were negative. There was no polyhydramnios. Fetal ultrasound showed normal cardiac anatomy and no fetal oedema. Complete heart block was evident, with an atrial rate of 125 beats/min and ventricular rate 60–65 beats/min. Premature labour was controlled with terbutaline at 32 weeks. Spontaneous labour and rupture of membranes occurred at 36 weeks gestation. External fetal heart rate monitoring tracked normal atrial responses to uterine contractions through labour. A 2700 g female infant was born spontaneously. The electrocardiogram showed complete heart block, with a rate of 60–65 beats/min. There was no evidence of congenital heart disease or congestive heart failure. This infant was discharged from the neonatal nursery in good condition.

Patient no. 5

A 25-year-old primigravida was referred at 36 weeks gestation because of fetal bradycardia of 60 beats/min. Maternal medical history, ANA and Anti-Ro titres were negative. There was no evidence of polyhydramnios. Fetal ultrasound showed normal cardiac anatomy and no fetal oedema. Echocardiography of the fetus demonstrated complete heart block, with atrial rates varying between 120 and 130 beats/min. The fetal ventricular rate was 60. The mother was admitted at term in early labour. External fetal monitoring demonstrated normal variability in atrial rate. A variable deceleration, probably secondary to cord compression, was noted. The woman chose caesarean delivery. The newborn female baby weighed 2800 g. The electrocardiogram showed a broad QRS-complex idioventricular rhythm at a rate of 45–50 beats/min. This infant is doing well following insertion of a permanent epicardial ventricular pacemaker.

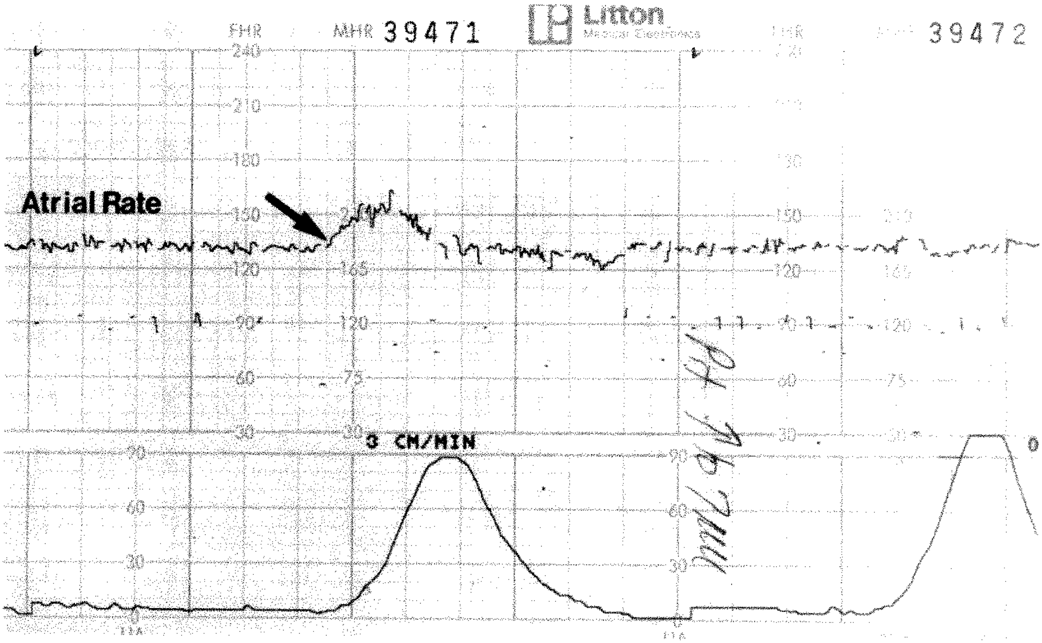

Fig. 3. External fetal heart rate monitor strip in patient no. 3 showing an atrial rate of 130–140 beats/min, with normal rate reactivity in response to uterine contractions (→) (lower curve represents uterine activity).

Discussion

The application of fetal heart rate monitoring for the assessment of fetal well-being has been widely accepted by perinatologists in many countries (Dawes 1985). The mean fetal heart rate results from the interplay of several factors, including the intrinsic pacemaker rate of the sinoatrial node, mean parasympathetic tone and phasic alterations in sympathetic tone. Beat-to-beat variability of fetal heart rate is an important property, despite the lack of certainty regarding the underlying mechanism.

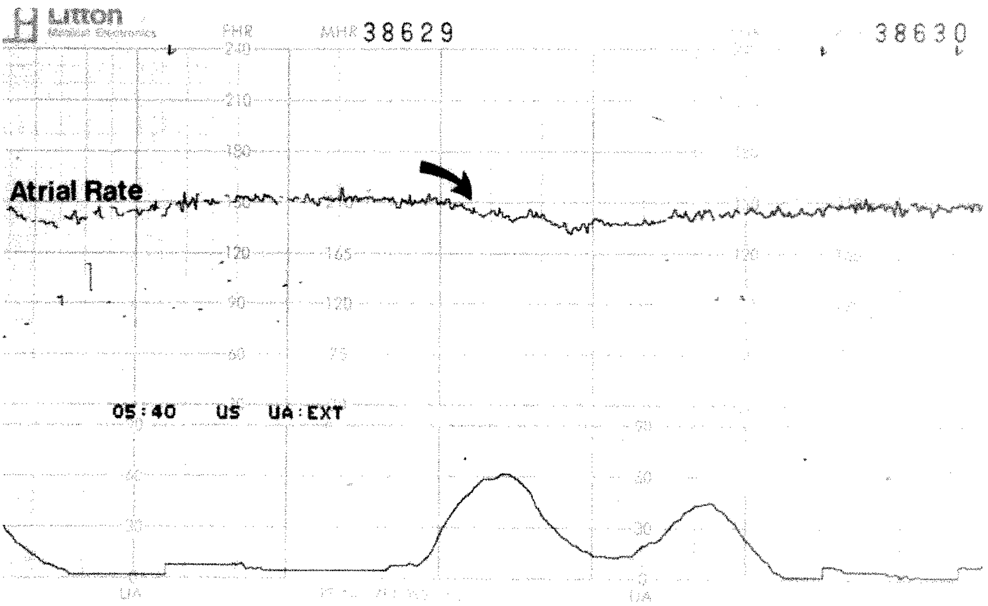

Fig. 4. External fetal heart rate monitor strip from this fetus suggesting late deceleration in atrial rate (→) prompted decision to perform caesarean delivery.

It is suggested from fetal animal studies that there is vagal innervation of the sinoatrial node as well as the atrioventricular nodal region. Administration of atropine increases the baseline heart rate and abolishes rate variability, suggesting the existence of a 'baseline' vagal tone with heart rate variability secondary to phasic alterations in parasympathetic stimulation (Mendez-Bauer *et al.* 1963; Schifferli & Caldeyro-Barcia 1973). From studies with propranolol it is suggested that there is sympathetic influence on fetal heart rate and force of cardiac contraction (Llanos *et al.* 1980). Because atropine almost completely abolishes fetal heart rate variability and propranolol alters variability only minimally, it is thought that fetal heart rate variability in the primate is modulated primarily by alteration in vagal tone.

Hypoxia or hypercapnia cause fetal bradycardia and hypertension (Parer 1983) via the fetal central nervous system or by a direct effect of hypoxia upon pacemaker tissue (Stowe *et al.* 1985). Moderate (≥ 100 beats/min), prolonged (> 2 min) bradycardia, with maintenance of fetal heart rate variability, is probably not associated with fetal acidosis (Parer 1983). Below 80 beats/min, prolonged bradycardia may be related to fetal asphyxia. The latter results ultimately in the abolition of fetal heart rate variability. For this reason, fetal bradycardia below 80 beats/min is frequently considered sufficient cause for immediate, often caesarean, delivery.

The application of echocardiographic techniques for the analysis of atrioventricular contraction sequence has enabled us, in a subgroup of fetuses with atrioventricular block, to distinguish the difference between bradycardia secondary to sinus slowing (presumably the mechanism referred to in the paragraph above) and bradycardia secondary to impaired atrioventricular conduction. In the latter situation the M-mode echocardiogram, pulsed Doppler scan, or external heart rate monitoring oriented using fetal echocardiographic images, may be used to assess atrial rate and its variations, even if the ventricular rate shows less variability. The principle of monitoring atrial rate as a barometer of adequacy of cardiac output has been applied for over 20 years in assessing pacemaker therapy in patients with complete heart block (Bevegard 1962; Mitsui *et al.* 1969).

In our first patient, the ventricular rate varied normally around the slow baseline rate. This variability of a pacemaker in the region of the atrioventricular node may have been mediated by variations in parasympathetic tone and/or the sympathetic nervous system. Conversely, in the fifth patient the broad-QRS-complex idioventricular rhythm appeared to arise from a considerably 'lower' portion of the fetal heart, and was seemingly unresponsive to variations in vagal tone, despite evidence of atrial reactivity.

In the presence of compensatory dilation of the fetal heart (and an increase in stroke volume), bradycardia need not be associated with inadequate cardiac output, and therefore we may expect fetal heart rate changes (either the ventricular or the atrial rate) to remain a valuable barometer of fetal well-being, despite the low baseline ventricular rate. In light of information suggesting a limited Frank–Starling response of the fetal heart (Rudolph & Heymann 1976), the bradycardic fetus with dilated ventricles may have decreased cardiac 'reserve'. In such cases cardiac decompensation may appear quite suddenly, necessitating close, continued intrapartum monitoring of fetal well-being. In the case of second degree atrioventricular block, despite the low ventricular baseline rate, the ventricular rate 'tracks' the atrial rate, and 'routine' fetal heart rate monitoring may actually assess fetal heart rate variability. After our first experience with the fetal echocardiographic diagnosis of complete heart block, we reviewed the records of 14 patients in our paediatric cardiology clinic with congenital complete atrioventricular block and found that all had been delivered by caesarean section. In only four patients did our chart review uncover the indication for operative delivery. In each case the indication was 'fetal bradycardia'.

Approximately 30% of newborn infants with congenital complete heart block have associated heart disease, in most cases structural heart disease. Approximately 10% of newborn infants with congenital complete heart block die. Most mortality occurs in the group with associated heart disease, profound bradycardia (below 50–55 beats/min) or evidence of congestive heart failure. For this reason the presence of congestive heart failure, profound bradycardia or structural heart disease are the prime indications for pacemaker insertion in affected newborn but this represents the minority of the patients with congenital heart block (Hoffman 1971; Michaelsson & Engle 1972).

Two-dimensional fetal echocardiography may enable recognition of structural heart disease and assessment of cardiac dimensions to determine whether there has been an increased ventricular stroke volume to compensate for fetal bradycardia. M-mode echocardiography, pulsed-Doppler echocardiography and continuous wave Doppler external fetal heart rate monitoring may then be used to assess fetal atrial rate variability, even if ventricular response rate does not 'track' with the atrial rate. Using these techniques it may be possible, in many such cases, to avoid 'routine' caesarean delivery.

It should be emphasized that using M-mode echocardiography to track atrial rate throughout labour, while feasible, is very tedious. We prefer to use external (continuous wave) Doppler monitoring of atrial activity and/or directly-applied scalp electrodes to the presenting fetal part, providing a direct electrocardiographic monitor of atrial and ventricular activity.

Due to the limitation in fetal cardiovascular 'reserve' in the bradycardic fetus, which could predispose to a sudden and dramatic deterioration in fetal well-being, we also recommend fetal scalp pH monitoring when vaginal delivery is considered (Kubli *et al.* 1969).

In conclusion, echocardiographic imaging can be used to assess cardiac structure in tandem with M-mode, pulsed Doppler and continuous wave Doppler external fetal heart rate monitoring; fetal atrial rate alterations may be assessed in fetuses with bradycardia due to varying degrees of atrioventricular block. In such patients the fetal sinoatrial node remains under control of the fetal central nervous system, with parasympathetic and sympathetic influences altering the atrial rate in a normal fashion, despite the fact that the ventricle may not 'track' atrial activity. In such patients careful monitoring with these techniques, along with scalp electrode electrocardiography and scalp pH sampling, may avoid the need for 'routine' caesarean delivery, while providing a safe means of assessing fetal well-being.

Acknowledgments

This work was supported by Clinical Research Grant No. 6-225 from the March of Dimes Birth Defects Foundation, Mamaroneck, New York.

Dr Copel is Kennedy Dannreuther Foundation Fellow of the American Association of Obstetrics and Gynecology Foundation

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Received 18 August 1986
Accepted 2 December 1986

British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp 975–978

Pelvic examination: a survey of British practice

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Summary. Of 850 consultant gynaecologists in Great Britain who were asked about their preferred method of pelvic examination, 777 (91%) replied including 87 women. Of these, 574 (74%) regularly choose the dorsal position both for bimanual and speculum examination although 227 of this group use the lateral position in some circumstances. The other 203 (26%) preferred the left lateral for routine speculum examination and 100 of them also regularly used that position for bimanual palpation. There were marked regional variations in clinical practice, the lateral position being broadly more favoured in the South than in the North. The age of the gynaecologist was an important factor but practical clinical considerations appeared to be less important than habit and upbringing in determining choice of method.

This survey of everyday clinical practice was prompted by concern about the standard of pelvic examination shown by candidates at MB finals and in the MRCOG. This applies particularly to the use of the vaginal speculum which, even allowing for examination nerves, often appears clumsy and uncomfortable for the patient especially when used in the dorsal rather than in the lateral position.

A preliminary brief communication (Amias 1984) produced a minimal response, so a simple questionnaire was sent to the 850 consultant gynaecologists in Great Britain listed in the Medical Directory 1984 along the following lines:

(1) When you carry out a routine bimanual examination on a conscious patient, in which position is she usually lying?
  Dorsal (supine)
  Left lateral
(2) When you carry out a routine speculum examination on a conscious patient:
(a) Which instrument is your usual first choice?
  Bivalve (Cusco's type)
  Duckbilled (Sims' type)
(b) In which position do you usually place your patient?
  Dorsal (supine)
  Left lateral

Additional comments were invited under each subheading.

Results

Replies were received from 777 (91%) including 87 women, with a large volume of added comment. A number of respondents took exception to the use of the term 'duckbilled' as synonymous with the Sims' speculum rather than with the bivalve type but standard textbooks endorse the author's view.

For bimanual and speculum examination there was a clear first preference for the supine position with 574 (74%), compared with 203 (26%) who favoured the lateral position.

Among the 'lateral thinkers' 100 used that position both for bimanual and speculum examination and 103 for speculum only. It might have been expected that women gynaecologists would favour the dorsal position compared with the group as a whole but this was not the case and the spread was similar with 76% of 87 women gynaecologists preferring the dorsal position.

Within the group favouring the dorsal position 347 (45% of the whole) claimed to use that position invariably but the remaining 227 (29% of the whole) used the lateral mode in special circumstances—notably prolapse. There was a

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Table 1. Percentage of 'laterals' by region

Region	Total	'Laterals' (%)
S Western	34	26
Wessex	36	55
Oxford	30	33
SW Thames	38	39
NW Thames	57	39
SE Thames	54	31
NE Thames	65	32
E Anglia	32	22
W Midlands	57	10
Wales	38	29
Mersey	29	65
Trent	52	21
Yorks	42	21
N Western	57	21
Northern	54	22
Scotland	102	2
Mean (%)	777	26

heavy bias throughout the series towards the use of the bivalve speculum as the instrument of first choice, but a valid comparative figure was most clearly established within the lateral preference group where the ratio of bivalve to Sims' type was 3:1. The practice within the dorsal majority was less easy to quantify because although the 'habituals', as anticipated, universally preferred the bivalve instrument, those who vary the position—commonly for patients with prolapse—only occasionally stated that they change to a different speculum, e.g 'generally: dorsal plus Cusco, for prolapse: lateral plus Sims' '. Mostly the comment was far briefer, e.g. 'dorsal unless prolapse'. Taking this into account it is estimated that about 85% of consultants in Great Britain use a bivalve speculum in all clinical circumstances.

Regional variations are striking Table 1 shows the percentage of lateral thinkers by region taking the 14 National Health Service regions of England with Wales and Scotland each as a single region. The data indicate that the lateral position is considerably more popular in the South of Britain than in the North. It will be seen, however, that there are maverick results in Wessex (55%) and Mersey (65%) on the one hand and West Midlands (10%) and Scotland (2%) on the other.

A number of comments suggested that age would account for individual preference and this led to a division of the response into three groups based on the year of obtaining the MRCOG The overall percentage in each age group and the range within the regions is shown in Table 2. The respondents were grouped according to the year they became MRCOG. The dorsal position was preferred by 53, 71 and 85% of those becoming MRCOG in 1947–59, 1960–69 and 1970–80, respectively. This partly explains the regional differences. Figure 1 shows an appropriate clustering of more lateral users among the older gynaecologists (Group A) with the notable exception of the four maverick regions.

These exceptions are interesting and may be due purely to chance though it is tempting to suggest an influence stemming from the local university centre There is some hard evidence for this in Mersey Region where the high percentage of lateralists (65%) commonly mentioned the Liverpool speculum—a narrow-bladed modification of the Sims' much in use in that part of the country but little elsewhere. On the other hand, the high proportion in Wessex may be a reflection not so much of the influence of Southampton teaching as of the generally high lateral preference in the South of England Scotland is strikingly different with 100 out of 102 consultants dedicated dorsalists and supplying several pungent and forthright comments in support of their practice to the general effect that the left lateral is an 'English position' and that

Table 2. Year of obtaining MRCOG—percentage by region

	Year of obtaining MRCOG		
Region	1947–1959 Group A (n=131)	1960–1969 Group B (n=328)	1970–1980 Group C (n=318)
S Western	15	41	44
Wessex	14	55	31
Oxford	16	37	47
SW Thames	21	45	34
NW Thames	21	47	32
SE Thames	17	39	44
NE Thames	23	43	34
E Anglia	9	41	50
W Midlands	7	47	46
Wales	13	42	45
Mersey	24	45	31
Trent	15	33	52
Yorks	14	41	45
N Western	19	39	42
Northern	15	39	46
Scotland	20	43	37
Mean (%)	17	42	41

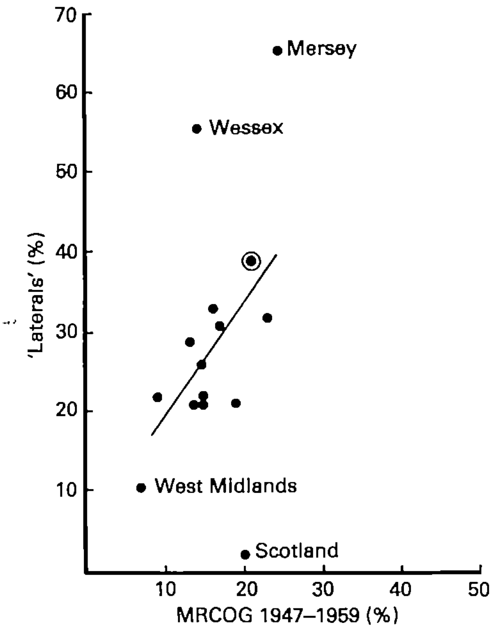

Fig. 1. Percentage of 'lateralists'/percentage of Group A consultants by region

the dorsal position is 'customary in Scotland' This suggests a strong and homogeneous university influence north of the border

The gratifying response of 91% to the questionnaire was maintained in the willingness of consultants to flesh out their replies with a wealth of additional comment and opinion providing more than a glimpse of current British gynaecological practice. Such information can be divided broadly into three groups.

Doctor–patient relation

Dorsalists claimed that the supine position was 'more comfortable and less embarrassing' and provided the opportunity for eye-to-eye contact during the examination. The lateral position was described as 'undignified' and 'a relic of Victorian prudery'. Lateralists argued, on the contrary, that *their* position was 'more comfortable and less embarrassing' allowing more cover and modesty and avoiding 'open display' especially in the presence of students Some women seemed to accept the lateral position much more readily than the dorsal, particularly the shy or nervous, including young girls, older nulliparae and members of certain ethnic minorities—such as those of the Muslim faith. The effect of custom and expectation from opposite standpoints can be crystallized in the comments. 'West Country patients are most cooperative' (dorsalist) and 'older ('county') ladies roll over without being asked' (lateralist).

Practical considerations

A number of dorsal examiners referred to the problems encountered in a busy out-patient department such as the limitations of clinic layout, the 'sheer numbers' to be seen and therefore the need for speed influencing the mode of examination and implying that in more leisured circumstances they would have used the lateral position at least for the speculum examination. Others advanced stronger clinical reasons for their preference such as the advantage of symmetry and gravity when the patient is supine, the easier examination of the obese, the more satisfactory palpation of the vaginal fornices—especially the left, the ability to inspect the vulva more readily in the dorsal position and to perform simple procedures such as the taking of swabs and smears, cryosurgery and the insertion of contraceptive devices (IUCDs).

These latter advantages were equally firmly claimed for the lateral position, particularly with regard to the ease of insertion of IUCDs, fitting of diaphragms and pessaries and for Vabra aspiration. Lateralists also stated that obese women were easier to examine on the left side, especially for vulval inspection and palpation of the pouch of Douglas though it was admitted that a small mass on the left side of the pelvis would be easier to palpate dorsally.

The lateral position was found to be particularly useful for patients with limited hip abduction due to arthritis or injury and those with cardiac or respiratory disease who invariably preferred to lie on their left side rather than in dorsal discomfort.

The widest support for the lateral position concerned its value in the assessment of prolapse and urinary incontinence and such cases were the commonest reason for variation within the dorsal preference. The ability to view the upper vagina and cervix, to seek causes for incontinence including fistula and to inspect each vaginal wall in turn were considered to outweigh the advantage of gravity in a dorsal assessment particularly when a Sims' type speculum was preferred or a bivalve with a light source in the handle (e.g. Brewer, Semm). Similarly the lateral position was strongly advocated for planning the route for hysterectomy, in the post-operative review of repair operations, in recurrent prolapse and, most importantly, for cancer follow-up when rectal as well as vaginal examination is necessary.

General comments

Under this heading were observations of a general nature referring to the imprint of early training, habit, the influence of postgraduate institutions and the admission by several that they examine with one position but teach the other. A few offered compelling personal reasons for choice of practice, for example 'I am left-handed', 'I am a female with very small hands' (dorsalists); 'I am 6′ 7″' (lateralist). Within this section too should be included expressions of opinion with or without further explanation. One dorsalist stated simply that 'the left lateral is old-fashioned' and another, with breathtaking hyperbole, that it was 'the ruination of British gynaecology'. Comments varied between the terse and the lengthy, sometimes with explanatory drawings and historical references and in several cases offering advice and encouragement to expand the enquiry in one or other direction. Most appeared to be intrigued with the idea of such a survey and only four could see no point at all and expressed their opinion in abusive terms.

Discussion and conclusions

It is illuminating to ask one's colleagues and oneself questions about basic clinical practice, and helpful to think again about something we are doing every day. When consultant status is reached it becomes increasingly difficult to keep in touch with the practice of others, even within the same hospital or district. The general conclusion from this enquiry is that, despite the variety of practical reasons advanced, our method of pelvic examination is dictated more by habit and upbringing than by specific clinical need.

Over half of the consultant gynaecologists in Great Britain use the lateral position on some occasions and one quarter regularly, the bivalve speculum being the commonest in general use. Six varieties of the basic Cusco type were mentioned amongst the replies, but in whichever modification the instrument is designed so that what is intended to be the posterior blade rotates, swivels or slides on the anterior blade which is one piece with the viewing aperture. Thus pressure is exerted not forward against the highly sensitive urethra, clitoris and mons pubis, but backwards against the less sensitive posterior vaginal wall and perineum, allowing the handles, ratchet or screws to be perineal rather than pubic.

Pelvic instruction at undergraduate level is best introduced in the operating room and continued in the out-patient clinic on a 1:1:1 (doctor:patient:student) basis. At postgraduate level it must not be assumed that new trainees are well versed in basic clinical method which should be supervised and if necessary retaught as for medical students. In the clinical part of the MRCOG enough time and care should be taken to ensure that the candidate has an acceptable clinical technique and that theory takes second place to practice in that part of the examination.

Whichever method of pelvic assessment we adopt for regular use, students should be taught sensitivity in carrying out what is for the doctor a commonplace but for the patient at best an unwelcome ordeal.

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Received 29 October 1986
Accepted 11 February 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol. 94, pp. 979–984

Isolation of *Gardnerella vaginalis* in pure culture from the uterine cavity of patients with irregular bleedings

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Summary. Hysterectomy was performed in three patients because of persistent irregular vaginal bleeding. Before the operation samples were taken from the cervical os for cultivation of *Gardnerella vaginalis,* yeasts, viruses, *Chlamydia trachomatis,* and aerobic and anaerobic bacteria. Immediately after the operation, the uterus was opened under sterile conditions and samples obtained from the isthmus and fundus of the uterine cavity were examined microbiologically. In all three patients *G. vaginalis* was grown in pure culture from the fundus. Serum antibody titres against *G. vaginalis* were significantly raised in all three patients, and histology revealed mononuclear cells in the endometrium. The isolation of *G. vaginalis* from the endometrium of patients with clinical and histological signs of inflammation and with antibodies to *G. vaginalis* in serum indicates that the organism may play a causative role in endometritis.

More than 70 years ago, Curtis (1914) reported the recovery of a Gram-negative bacterium from patients with purulent vaginal discharge. The organism was given the name *Haemophilus vaginalis* by Gardner & Dukes (1955) who isolated it from 92% of women with non-specific vaginitis, since it seemed to require a factor present in blood for growth. After further examination of the growth characteristics and morphology (Zinnemann & Turner 1963), it was placed in the genus *Corynebacterium* before being assigned to a novel genus and species, *Gardnerella vaginalis* (Greenwood & Pickett 1980).

During these years several studies have tried to incriminate the bacterium as a causative agent in vaginitis, urethritis and puerperal infection. Recovery of *G. vaginalis* from the upper genital tract and its possible role in endometritis have not been described to our knowledge. In the present study we isolated *G. vaginalis* in pure culture from the upper part of the uterine cavity in three patients with clinical and histological signs of endometritis.

Patients and methods

The patients were admitted to the Department of Gynaecology, University Hospital, Aarhus, Denmark for hysterectomy because of persistent irregular bleeding as described in detail below.

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Microbiological methods

The specimens for *G. vaginalis* were cultured on a selective and differential bi-layer medium (HBT agar) containing 5% human blood and 0·0075% Tween 80 (Totten *et al.* 1982) and also on agar with nitrofurantoin, sulphonamide and nitronidazole sensitivity tablets (Rosco). The plates were incubated at 35°C for at least 48 h in an anaerobic cabinet. *G. vaginalis* was identified as Gram-negative or Gram-variable, short pleomorphic rods with a characteristic β-haemolysis and colony morphology on HBT agar with negative catalase and oxidase reaction and with a characteristic sensitivity pattern (Piot *et al.* 1982). *Chlamydia trachomatis* was cultured using cycloheximide-treated McCoy cells (Ripa & Mårdh 1977). The culture technique for yeasts (Lodder 1971), viruses and anaerobic and aerobic bacteria (Lennette *et al.* 1980) has been described in detail by others

Sampling technique

Cervical specimens. Samples for culture were collected immediately before the hysterectomy by rotating swabs into the cervical canal after the cervical os had been exposed with a sterile vaginal speculum. Samples for *G. vaginalis* were taken with cotton-tipped wooden sticks treated with charcoal and transported to the laboratory in Stuart's medium. Specimens for *C. trachomatis* were collected with cotton-tipped swabs (ENT, Medical Wire and Equipment, Corsham, UK), for viruses with cotton-tipped wooden sticks, for yeasts and for aerobic and anaerobic bacteria with cotton-tipped wooden swabs treated with charcoal.

Endometrial specimens. Immediately after hysterectomy the uterus was opened by incising the fundus between the uterine cornua and then cutting from one cornu along the lateral margin of the uterus to the cervical os—to avoid contamination from the cervix. Swabs were taken from the isthmus and the posterior surface of the mucosa leaving the anterior surface undamaged for histological examination.

Histological techniques

Sections for microscopy were taken from the cervix, isthmus, mid-corpus and from one of the uterine cornu The biopsies were processed by routine methods. The stains used were haematoxylin and eosin, Giemsa and Unna-Pappenheim.

Serology

The presence of antibodies of *G. vaginalis* in the sera was measured by a micro-immunofluorescence technique (Wang *et al.* 1977) with the modification that the *G. vaginalis* antigens were not formalized. In brief, the bacteria was suspended in PBS at a concentration of 1 × 10^9 cfu/ml (colony forming units/ml) mixed with an equal volume of 7% yolk sac, and antigen dots were applied to the wells of teflon-coated slides using a mapping pen. The antigen dots were air-dried, fixed with acetone and overlayed with serial dilutions of human antiserum. After incubation at 37°C in a moist chamber for 60 min, the slides were washed in PBS and overlayed with fluorescein-conjugated goat anti-human immunoglobulin (Miles, Slough). The slides were incubated as above for 60 min, washed in PBS, dried in air and examined under an epifluorescence microscope. The antibody titre was recorded as the reciprocal of the highest dilution of serum at which the bacteria fluoresced A titre of 16 or more was regarded as positive.

Findings

Patient 1

A 44-year-old nulliparous woman with no history of pelvic inflammatory disease (PID) or sterility was admitted for hysterectomy. She had a 2-year history of a combined meno- and metrorrhagia causing anaemia. During the previous 6 months an increased vaginal discharge and dyspareunia had occurred. Treatment with topical fungicides was unsuccessful. Six months before admission a currettage had been performed with only temporary effect on the bleedings. When admitted to the hospital, pelvic examination showed the uterus enlarged to double the normal size. No palpable masses or tenderness were found in the adnexae, but a slight tenderness was confined to the uterus. Erythrocyte sedimentation rate (ESR) was 1 mm/h. Hysterectomy was performed and the postoperative course was uneventful. The uterus was myomatous and measured 8 × 7 × 5 cm. Histology of the endometrium showed most glands in the secretory phase (Figs 1 and 2). The

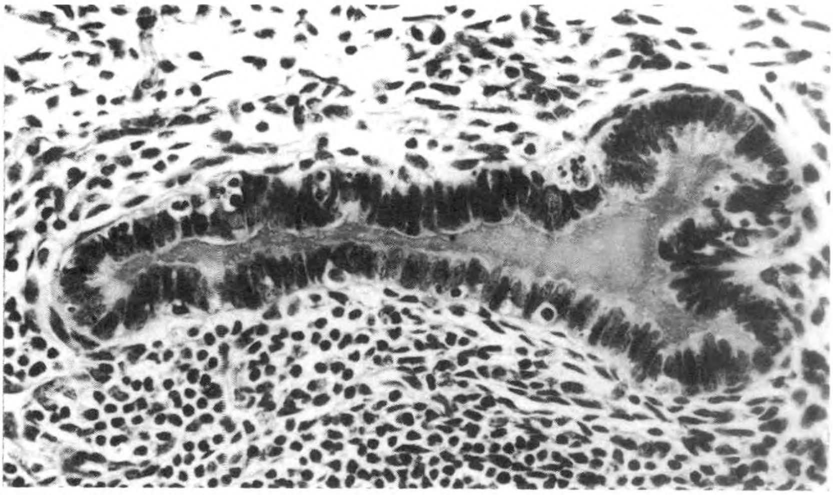

Fig. 1. Patient 1. A gland in stratum basalis containing highly eosinophilic material in the lumen and nuclear debris in the epithelial cells. An aggregation of lymphocytes is seen at the bottom. Haematoxylin and eosin × 360.

secretion in some lumina was highly eosinophilic. In some of the epithelial cells dark intracytoplasmatic inclusions were seen. No glands contained pus but occasionally a few lymphocytes were seen. The stroma was oedematous, focally with pseudodecidual reaction and with lymphocytes forming small aggregations deep in the mucosa. No plasma cells were seen. Culture from the cervix grew a mixed bacterial flora including *G. vaginalis*. The isthmus was sterile, but a pure culture of *G. vaginalis* was obtained from the uterine cavity. No other organisms were grown from the cavity. An antibody titre of 256 against *G. vaginalis* was measured in the serum.

Patient 2

A 48-year-old woman, para 3, was admitted because of irregular bleedings for 4 years starting as menorrhagia after discontinuation of oral contraceptives. During the last 12 months before admission the bleedings had changed to metrorrhagia. Several curettages had not revealed

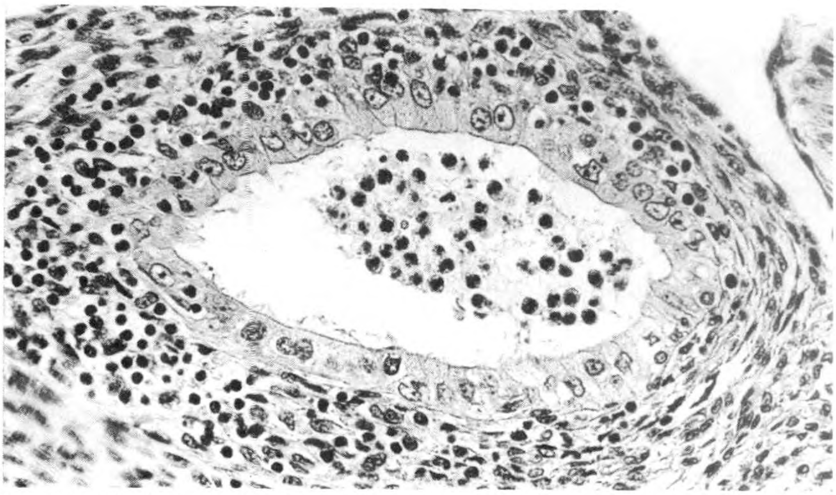

Fig. 2. Patient 1. A gland containing lymphocytes and surrounded by a narrow mantle of lymphocytes. The epithelium shows some degree of ciliated metaplasia. Haematoxylin and eosin × 360.

pathological changes of the endometrium. No hormonal therapy had been given during the previous 4 years. The last bleeding episode started 10 days before admission. At that time general examination was normal and pelvic examination did not disclose any abnormalities. Hysterectomy was performed and the postoperative course was uneventful.

The uterus was found to contain a submucous fibromyoma 2 cm in diameter. The endometrium was macroscopically normal. On microscopy most endometrial glands were secreting but some were proliferating and slightly hyperplastic (Fig. 3). Focally the epithelial cells were enlarged, pale and contained granular inclusions which could also be seen in the juxtaglandular stroma. Lymphocytes and a few plasma cells were found scattered or in small aggregations in the spindle celled stroma. Cultures from the cervix grew bacteria normally found in the vagina including *G. vaginalis*. From the isthmus and cavity of the uterus *G. vaginalis* was grown in pure culture. An antibody titre of 512 to *G. vaginalis* was found in the serum.

Patient 3

A 39-year-old woman, para 3, was admitted to the hospital because of a 4-year history of irregular bleedings. The patient had had a currettage $3\frac{1}{2}$ years previously. On that occasion the patient was sterilized by laparoscopy. Menorrhagia and irregular spotting gradually became worse. On admission the period lasted for 8 days with 3 days of very heavy bleeding. Pelvic examination showed a uterus of normal size but very tender. No palpable masses or tenderness were found in the adnexae. Hysterectomy was performed without operative or postoperative complications. The uterus measured 8 × 5 × 4 cm and was macroscopically normal.

Microscopically the endometrium was in the midproliferative phase. Some glands, especially those deeply located, were slightly hyperplastic (Fig. 4). Some epithelial cells contained dark inclusions. The stromal cells were spindle shaped. Small collections of lymphocytes and histiocytes were seen, some forming follicles. Plasma cells were present in one of the lymphatic follicles. Cultures from the cervix revealed growth of bacteria normally isolated from this site, including *G. vaginalis* which was also isolated in pure culture from the isthmus and fundus. The serum antibody titre against *G. vaginalis* was found to be 64.

Discussion

The uterine cavity is generally regarded as sterile. Ansbacher *et al.* (1967) tested the sterility of the uterine cavity in 78 patients by obtaining direct cultures from the cavity immediately after hysterectomy. They found that the presence of carcinoma of the cervix may predispose the uterine cavity to microbial invasion as 4 of 5 culture-positive patients had this condition. Bacteria were grown from the uterine cavity in only one patient without malignant disease. Likewise

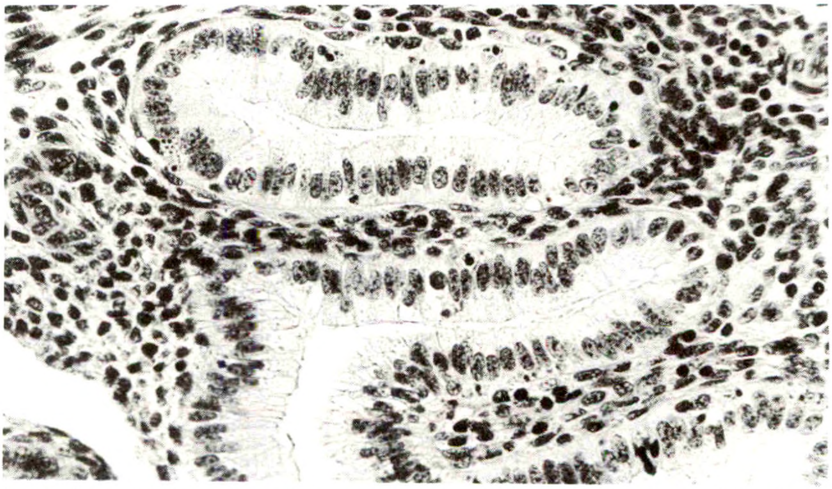

Fig. 3. Patient 2. Secretory phase glands with nuclear debris in the epithelial cells and scattered lymphocytes and plasma cells in the stroma. Haematoxylin and eosin × 360.

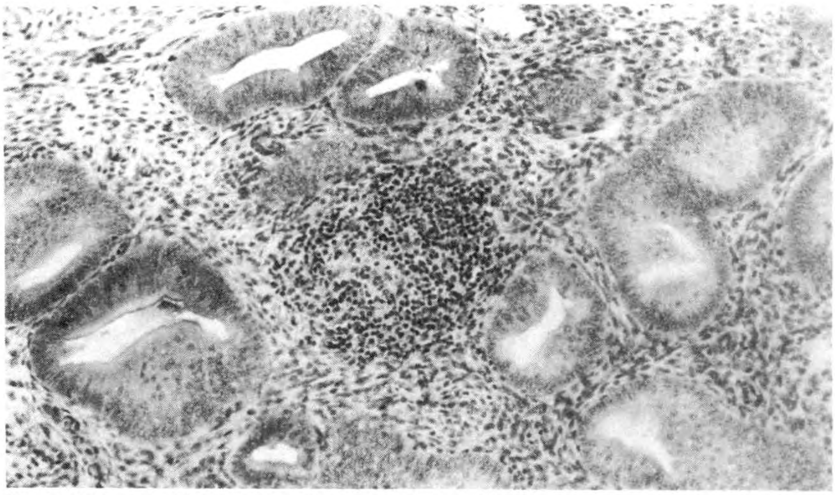

Fig. 4. Patient 3. Slightly hyperplastic glands deep in the mucosa surrounding a lymphatic follicle. No plasma cells are present. Haematoxylin and eosin × 125.

Spore *et al.* (1970) found that only 1 of 26 transfundal aspirates from the cavity contained bacteria. A few studies have reported a high recovery rate of bacteria from the uterine cavity. Thus, Bollinger (1964) reported that positive bacteriological cultures were obtained from the uterine cavity of 60% of 200 normal women. But, in this and other studies which reported high isolation rates from the uterine cavity (Calman & Gibson 1954; Hite *et al.* 1947), the samples were obtained by introducing a swab or aspiration device through a cannula inserted via the cervical os. The possibility of introducing bacteria into the uterine cavity from the lower genital tract cannot be excluded in these investigations.

Intrauterine contraceptive devices (IUCD) seem to allow vaginal bacteria to pass into the uterus along the tail of the device. Thus, Sparks *et al.* (1981) reported bacterial contamination of the uterine cavity in 15 of 17 patients with a tailed IUCD, whereas five uteruses with a tailless device were sterile. In three of the patients *G. vaginalis* was recovered from the uterine cavity, whereas an inflammatory reaction of the endometrium was not reported. In the present study three patients, who underwent hysterectomy because of irregular bleedings, harboured *G. vaginalis* in the fundus of the uterine cavity. Although all three patients were culture-positive for *G. vaginalis* from the cervix it seems unlikely that the occurrence of the organism in the fundus could be due to contamination from the lower genital tract because of the sterile technique used. Also, culture from one of the patients was negative from the isthmus uteri. All three patients showed aggregation of lymphocytes deep in the mucosa, some forming follicles with histiocytes. The lymphocytes were often of the immunoblastic type, some being pyroninophilic. In one patient no plasma cells were seen even after several supplementary sections were taken. All three patients presented clinical signs of endometritis characterized by irregular bleeding, but only two showed histological signs of endometritis characterized by inflammation with plasma cells. Some authors question whether plasma cells are a necessity for the diagnosis of endometritis (Novak & Woodruff 1979). Our findings seem to support this theory as one of the patients with obvious clinical signs of endometritis only had lymphocytes in the endometrium, when examined by histology.

Highly eosinophilic secretions in the gland lumina combined with dark inclusions in the epithelial cells as seen in patient 1 are mentioned by Govan (1962) as a minor lesion in tuberculous endometritis. The granules represent nuclear debris from stromal degeneration phagocytized by the epithelial cells (Dallenbach-Helweg & Poulsen 1985).

All three patients had significantly elevated serum antibody titres to *G. vaginalis*.

Hence isolation of *G. vaginalis* from the endometrium of patients with clinical and serological signs of inflammation seems to indicate that the organism may play a causative role in endometritis.

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Received 24 June 1986
Accepted 26 January 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp. 985–990

Individualization of patients for adjuvant chemotherapy after surgical treatment of cervical cancer

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Summary. Adjuvant chemotherapy using Tegafur (1-(2-tetra hydrofuryl)-5-fluorouracil) was given to 52 of 216 patients with recurrence risk of cervical cancer after primary surgical treatment, the degree of risk of recurrence having been formulated as a discriminant function by computer analysis of risk factors involved in disease recurrence. Using the formula, we have managed outpatients in three groups—no recurrence and recurrence after, and before 5 years. Under existing circumstances the power of the discriminant function we have achieved is not yet entirely satisfactory although clinically of value in patient management. Oral, long-term adjuvant chemotherapy in risk groups was of value, with a 37·4% instantaneous recurrence rate and mild side-effects. An instantaneous recurrence rate of 37·4% signifies that the recurrence rate in the group of patients given chemotherapy would be 37·4% if it were 100% in the patients not so treated—an improvement factor of just less than 3.

In order to obtain criteria for the chemotherapeutic management of patients after initial standard surgical treatment of cervical cancer, we have examined the main risk factors for recurrence. If the likelihood of recurrence can be reliably estimated, efforts can then be directed either to early detection of recurrence in those predicted as being at risk, or such patients can be given 'preventive' adjuvant chemotherapy. The principal factors related to risk of recurrence are given in Table 1.

Ideally, the best time to predict the risk of recurrence is at the time of primary treatment. We therefore analysed, for 236 patients from 1969–76, the relations between each individual's risk factors and her ascertained outcome, using quantification methods I, II and III (Goto *et al.* 1979) for predicting, discriminating, and/or classifying a phenomenon in respect of the surveyed or measured variables. Following this analysis, we used principal component analysis, or quantification method III (Goto *et al.* 1979), to clarify which are the most characteristic risk factors for cervical cancer recurrence. On the basis of our calculations, using the cases from 1969 to 1976, we were able to identify and classify high-risk patients. Subsequently, from 246 patients treated between 1977 and 1982, inclusive, we chose prospectively patients in intermediate and high-risk groups to be treated with adjuvant chemotherapy using comparatively low oral doses of Tegafur (1-(2-tetra hydrofuryl)-5-fluorouracil (Hiller 1964; Smart *et al* 1975). To estimate the effect of the chemotherapy, an instantaneous recurrence rate was calculated. This report describes our method of classifica-

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Table 1. Factors influencing post-surgical recurrence

Clinical stage	Tumour volume	Operative method
CIS	Level of invasion	Simple hysterectomy
Ia	Endometrial invasion	Semi-radical hysterectomy
Ib	Lymph node metastasis	Radical hysterectomy
IIb	Sites of localization	
IIIa		Operator
IIIb	CPL classification (Imai 1960)	A
IVa	C. Cirrhotic type	B
IVb	P. Progressive type	C
	L: Lymphatic permeation	D
Age (years)		E
≥60	Type of growth	
50–59	Exophytic	Degree of difficulty of operation
40–49	Endophytic	Length of operating time
≤39	Mixed	Amount of blood loss
Histological type	Degree of differentiation	Adjuvant chemotherapy
Squamous cell carcinoma	Well type	With
Adenocarcinoma	Intermediate type	Without
Adenosquamous cell carcinoma	Poor type	

tion into three risk-groups, brief results of follow-up of each group, and results of adjuvant chemotherapy.

Patients and methods

Analysis of patients, 1969–1976

There were 236 patients who had undergone radical hysterectomy (mostly combined with postoperative irradiation) for cervical cancer during the 8-year period 1969–1976, and who had been followed up for ≥5 years after the treatment. They were classified into the following groups: (1) no recurrence; (2) recurrence after 5 years; (3) recurrence before 5 years.

The reason why the high-risk patients were sub-divided into groups 2 and 3 was to detect the cases of especially high risk (group 3) as soon as possible after operation. They seem to have larger amounts of residual cancer than others and therefore need stricter follow-up at short intervals together with possible adjuvant chemotherapy.

Within each category, levels of invasion (classified into four levels of invasion of the cervical tissue and four levels of invasion of the parametrium) and the numbers of lymph node metastases were sub-classified, and an additional category, that of endometrial invasion (present or absent), was added to the categories employed previously. Analysis was performed using quantification method III (Goto *et al.* 1979).

Classification, treatment and follow-up of patients, 1977–1982

During the 5-year period 1977–1982 a total of 246 patients treated surgically (mostly combined with post-surgical irradiation) for cervical cancer (Stage Ib or higher) were classified into three groups according to the discriminant function, using their risk factors at the time of discharge: Group 1, no risk of recurrence is assumed; group 2, low possibility of recurrence is assumed; group 3, high possibility of recurrence is assumed.

Patients in group 1 did not receive adjuvant chemotherapy. Alternate patients in group 2 received Tegafur 400–600 mg/day orally for 3 years. Alternate patients in group 3 received Tegafur 400–600 mg/day orally for 5 years. The difference in the periods of chemotherapy between groups 2 and 3 is predicated on the possible quantities of residual cancer in each. Patients were examined periodically for recurrence by pelvic examination, vault cytology, colposcopy, blood screen and blood tumour markers, immune factors, chest X-rays, CT scan and 67 Ga or 99m TC scintigraphy.

Instantaneous recurrence rate using oral adjuvant chemotherapy in risk group

The effect of oral adjuvant chemotherapy was studied using multiple regression analysis for survival data, which allows for adjustment for prognostic factors described by Cox (1972).

Results

Principal component analysis

The following factors related to tumour size had high values on the X_1 axis: clinical stage, degree of invasion, tumour localization, lymph node metastases and endometrial invasion. The following pathological properties of the tumour had high values on the X_2 axis: histological type, CPL classification (Imai 1960) (C, cirrhotic; P, progressive; L, lymphatic permeation), and lymph node metastases. It was also apparent that coefficients in the X_1 axis were large in clinical stages IIIa and IIIb when: (a) the level of invasion was ≥5 blocks, (b) lymph node metastases were present, (c) a newly added category, endometrial invasion, was an important factor in the risk of recurrence. The analysis indicated that adenocarcinoma and adenosquamous cell carcinoma, the L type of the CPL classification by Imai (1960), deeply invading cancers, and those with multiple lymph node metastases all possess large coefficients and are strongly associated with a poor prognosis.

After analysing these factors the discriminant function was determined as $Z = 0{\cdot}810X_1 + 0{\cdot}710X_2$. The risk for group 1 is below 0·053, that for group 2 is 0·053–0·375 and for group 3 is over 0·375. The rates of overall concordance by means of the discriminant function were 78·5%. Using the same method, Okamura *et al.* (1980) obtained a concordance rate of 55·0%.

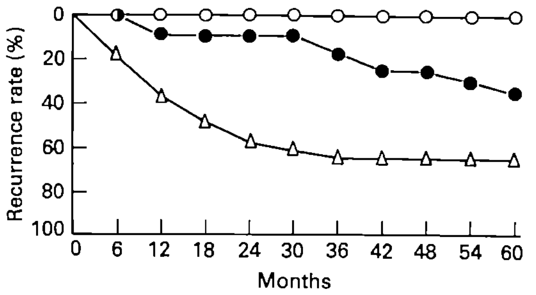

Fig. 1. Rate of recurrence in each risk-group ○, Risk-group 1 (n = 132); ●, risk-group 2 (n = 22), △, risk-group 3 (n = 92)

Numbers of patients in risk groups

The 246 patients from 1977–82 were classified prospectively into three risk groups: Group 1, 132 patients (53·7%) at no risk of recurrence within 5 years; group 2, 22 patients (8·9%) at 'low risk'; group 3, 92 patients (37·4%) at 'high risk'. There were no recurrences in group 1, 5 (22·7%) in group 2, and 52 (56·5%) in group 3 (Fig. 1). The differences are significant ($P<0{\cdot}01$). Recurrences developed after 1 year in group 2 and in <3 years in group 3.

Results of treatment with adjuvant chemotherapy

Adjuvant chemotherapy was given to 52 of the 114 patients in groups 2 and 3 (Fig. 2). A clear difference ($P<0{\cdot}01$) in recurrence rate was seen over 6–60 months. The recurrences in patients without chemotherapy occurred up to 60 months after the original surgery; no patient on chemotherapy had a recurrence later than 36 months after starting the drug. The rate of recurrence was 25% (13 patients) with chemotherapy, and 71% (44 patients) without chemotherapy.

Figure 3 shows the recurrence rates for patients with and without chemotherapy according to the risk value (Z). There were no recurrences in patients with a risk value of 0·053 or less. In patients without and with chemotherapy the rates were 30% and 20% respectively in group 2, with Z values of 0·053–0·375. In group 3, as the Z value rose the recurrence rate in patients not given chemotherapy increased markedly. On the other hand, the recurrence rate in patients given chemotherapy did not increase significantly, remaining at 30%

The instantaneous recurrence rate was calculated and Table 2 (Cox 1972) shows the estimated regression coefficients for the main prognostic factors, i.e. clinical stage, histological type, CPL classification, and lymph metastases (for each: $P \leq 0{\cdot}01$). The regression coefficient (β) for adjuvant chemotherapy was $-0{\cdot}9826$, so that the instantaneous recurrence rate $\lambda(t) = e^{\beta} = e^{-0{\cdot}9826} = 0{\cdot}374$. Thus, the estimated instantaneous recurrence rate of disease in the adjuvant chemotherapy group was 37·4% of that in the non-adjuvant chemotherapy group.

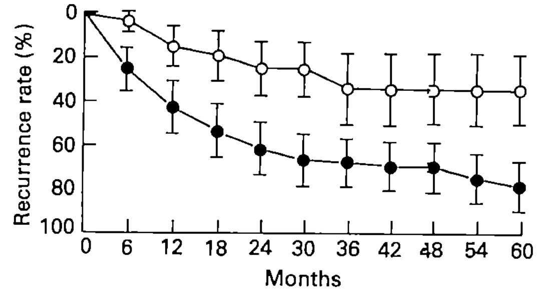

Fig. 2. Mean (±SD) rate of recurrence in risk-groups 2 and 3 combined with adjuvant chemotherapy ($n = 52$) (○) and without adjuvant chemotherapy ($n = 62$) (●)

Discussion

To evaluate the risk of recurrence after surgery, 236 cases of cervical cancer from 1969–76 were statistically examined and principal component analysis by the quantification III method was applied. Those factors related to the size of the tumour, i.e. clinical stage, level of invasion, tumour localization, and endometrial invasion, all had high values on the X_1 axis. Those factors related to pathological features, i.e. histological type, CPL classification, and lymph node metastases, had high values on the X_2 axis.

In recurrence risk, clinical stage and level of invasion are highly significant. Previously reported 5-year cure rates were 65% in those with and 98% in those without parametrial spread (Noguchi *et al.* 1981). In the present series parametrial spread was found in 39% of patients, 44% of whom had recurrent disease. In those without parametrial spread, the recurrence rate was only 17%. Clearly, parametrial involvement indicates an especially poor prognosis.

As regards tumour localization as a risk factor the present investigation showed that 16% of patients with carcinoma of the portio vaginalis, 21% of those with carcinoma of endocervix, and 33% of those with both had recurrences. Endocervical cancer has a relatively poor prognosis in that symptoms such as contact bleeding occur rather late and detection is thus delayed

Endometrial spread is an important factor in recurrence risk, our investigation showing it to be 21% of all cases. Mitani *et al.* (1964) reported that invasion of the corpus was found in 26%, and 5-year cures were 31% for those with, and 72% for those without, endometrial invasion.

Histological type has a high value on the X_2 axis. The prognosis of adenocarcinoma is worse than that of squamous cell carcinoma if the clinical stage is II or more, or if the carcinoma is treated by radiation (Kjöstadt 1977). Lymph node metastases of adenocarcinoma were more frequent than for squamous cell carcinoma (Swan 1973; Kottmeier 1976). In the present investigation, adenocarcinoma and adenosquamous cell carcinoma had a worse outlook than squamous cell carcinoma.

The histological definitions for the CPL classification proposed by Imai (1960) were originally as follows. Cirrhotic (C) type: regardless of the amount of connective tissue, direct contact between the malignant cells and healthy tissue, mainly muscle, not seen Progressive (P) type: direct contact seen. Lymphatic permeation (L) type: cancer cells present in the lymphatics or blood vessels. He also noted that the 5-year cure rate was 97% for C, 93% for P, but only 50% for L type cancers. Prognosis for the L type carcinoma is therefore very poor, 2·204 on the X_2 axis in the present series. Imai's classification is thus of some importance in evaluating prognosis

There are many reports about lymph node metastases. Odaka (1967) noted metastases in 25% of cases, our rate being the same and his 5-year cure rate was 66% for those with one, 25% with two, and 17% for those with three or more nodes involved, as compared with 54%, 50%, and 0% respectively in our series. Lymph node metastases thus indicate a poor prognosis; for two or more lymph nodes involved in the present cases, the X_2 axis value was very high, 3·1010.

To help determine prognosis, the discriminant function $Z = 0{\cdot}810X_1 + 0{\cdot}710X_2$ was deduced by using the many factors which affect each other in complicated interrelations capable of being calculated and used predictively. The rate of con-

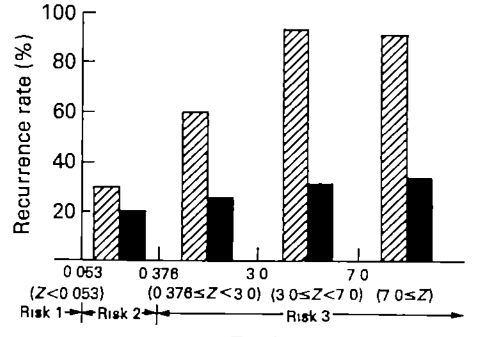

Fig. 3. Rate of recurrence and risk value (Z) ■, with adjuvant chemotherapy, ▨, without adjuvant chemotherapy

Table 2. Results of Cox regression analysis

Prognosis factors	Parameter of each prognosis factor (β)	Standard error of β	$\left(\frac{\beta}{SE}\right)^2$	Significance
Adjuvant chemotherapy				
(−)	0			
(+)	−0·9826	0·2324	17·8779	$P<0{\cdot}01$
Clinical stage				
Ib	0			
IIa+IIb	0·6597	0·2714	5·9063	$P<0{\cdot}05$
IIIa	1·1908	0·3379	12·4201	$P<0{\cdot}01$
Histology				
Squamous cell type	0			
Adenosquamous type	0·6519	0·2212	8·6887	$P<0{\cdot}01$
CPL classification				
C	0			
P	0·8397	0 3110	7·2900	$P<0{\cdot}01$
L	1·5509	0 2893	28·7374	$P<0{\cdot}01$
Lymph metastases				
0	0			
1	0·9372	0·2469	15·5317	$P<0{\cdot}01$
2	1·8084	0·2247	64·7407	$P<0{\cdot}01$

cordance by means of the function was 78·5%. Using a previously-derived function a concordance rate of 65·0% was obtained (Okamura *et al.* 1980), somewhat less than our own. To further improve the concordance rate and to reduce the false negative rate it is necessary to carry out the analysis in still more cases.

Prophylaxis against the recurrence of cancer after operation has long been tried by adjuvant chemotherapy—on breast cancer (Mrazek *et al.* 1959), stomach and intestine cancer (Moore *et al.* 1963; Higgins *et al.* 1971), and lung cancer (Karrar 1972). In postoperative chemotherapy the aim is either to kill residual cancer cells or to inhibit their regrowth. The Tegafur (Futorafur, Grünenthal; Fulaid, Takeda) used in the present series is an oral drug with few side-effects. It belongs to the group of agents in which cancer cells are killed at the S cycle-stage and protein synthesis is blocked at all other times in the cell cycle (Skipper *et al.* 1970); the cell-kill mechanism does not depend so much on the Tegafur concentration as on the contact time variable concentrations. The cell cycle times of cervical squamous cancer are shorter than those of other cancers (Gavasto & Pileri 1971; Skipper *et al.* 1970), but those of residual cervical cancer after primary treatment seem to be longer than before, presumably because of the large reduction in tumour volume and the influence of post operative radiation. For these reasons Tegafur was the chosen chemotherapy in the present series.

Randomization for chemotherapy was not thought necessary to find its effects because judgment of results is made from purely objective rather than subjective findings. Recurrence is obviously diagnosed by smear, biopsy, and tumour formation and not from slight changes of size in the recurrent tumour (Gehan & Freireich 1974). However, patients for chemotherapy were chosen alternately to remove bias due to known severity of disease Side-effects of the doses used were very mild and appeared to have no influence on host immunity.

The 246 patients (1977–1982) were classified prospectively into three groups. The 132 patients in risk-group 1 have had no recurrences; 5 of the 22 patients (23%) in risk-group 2 had recurrences; and of the 92 patients in risk-group 3, 52 (57%) have had recurrences ($P<0{\cdot}01$). Recurrences usually developed after 3 years in risk-group 2, and in <3 years in risk-group 3.

The estimated instantaneous recurrence rate demonstrating the chemotherapeutic effect was 37% of that for the non-chemotherapy group. These results appear to confirm the clinical value of Tegafur as adjuvant chemotherapy in patients at risk of recurrence of cervical cancer after primary surgical treatment.

Acknowledgments

For encouragement and advice I wish to thank Professor O. Sugimoto, G. H. Green FRCOG, and Dr M. Jamieson FRNZCOG (National Women's Hospital, New Zealand), and Mr H. Morikawa. I thank my colleagues for help with all the cases.

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Received 8 April 1986
Resubmitted 8 December 1986
Accepted 4 April 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol. 94, pp. 991–994

The prognostic significance of lymphatic vascular space invasion in endometrial adenocarcinoma

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Summary. In a histopathological review of 171 cases of endometrial adenocarcinoma, 42 neoplasms demonstrated lymphatic and/or vascular invasion. This finding was significantly correlated with depth of myometrial involvement and stage of disease at operation. Tumour cell type, and histological grade were correlated to a much lesser extent, whilst the patient's age bore no relation. Prognosis was significantly poorer in patients whose adenocarcinomas had invaded lymphatic and/or vascular spaces compared to those whose neoplasms had not. These observations emphasize the importance of considering lymphatic/vascular invasion in staging endometrial adenocarcinomas.

Prognostic criteria for endometrial adenocarcinoma, though reasonably well defined, still lack sufficient precision. Thus, in overall terms survival is clearly related to FIGO stage: nevertheless, approximately 20% of women with Stage 1 neoplasms will die of the disease and, because Stage 1 tumours predominate in any series of endometrial adenocarcinoma, a majority of deaths from this tumour occur in women who present with Stage 1 disease (Malkasion 1978; Beck 1979; McCabe & Sagerman 1979; Connelly *et al.* 1982; Lotocki *et al.* 1983; Christopherson *et al.* 1983; Di Saia *et al.* 1985). Histological grading is clearly of some prognostic value (Jones 1975; Connelly *et al.* 1982) but all currently used grading techniques suffer from the defects of being insufficiently discriminatory (a large majority of cases being Grade 1), based on subjective criteria, lacking well defined boundaries between the different grades and taking little account of heterogeneous patterns of differentiation within an individual neoplasm. The depth of myometrial invasion is often thought to be of considerable prognostic value (Jones 1975) but not all studies have confirmed this view (DePalo *et al.* 1982; Martin *et al.* 1983; Geisenger *et al.* 1986). Furthermore there is no agreement as to whether it is the depth from the endomyometrial junction which is important or the distance from the serosa (Lutz *et al.* 1978).

Invasion of lymphatic/vascular spaces by an endometrial adenocarcinoma has received only scant attention as a prognostic factor (Hanson *et al.* 1985); we report here a study of the prognostic significance of this histological finding.

Subjects and methods

Pathological material from 171 women treated for endometrial adenocarcinoma at St Mary's Hospital, Manchester was reviewed. In all cases the initial treatment had been surgical and hence hysterectomy specimens were available from all patients. An average of six blocks was available for each patient and haematoxylin and eosin stained sections were examined for the presence of lymphatic/vascular space invasion by tumour.

Lymphatic/vascular space invasion was only recorded as being present if tumour cells were seen within a space which had a definite and clearly identifiable endothelial lining.

The period of follow-up of the patients ranged from 6 months to 12 years but the majority of

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patients had been followed up for at least 5 years In most cases follow-up information was available from the hospital records but where this information was lacking postal questionnaires were sent to the patient's general practitioner.

Computerized statistical analysis of the data was performed using the χ^2-test on contingency tables to determine the significance of the various correlations with P<0·05 being considered significant. Survival was calculated from the date of operation according to the actuarial method of Kaplan & Meier (1958) Statistical significance was evaluated by the generalized Savage (Mantel-Cox) test.

Table 1. Lymphatic/vascular invasion in relation to histopathological variables of endometrial adenocarcinoma

	No of patients	Lymphatic/vascular invasion *n* (%)
Stage		
I	123	19 (15·4)
II	18	9 (50·0)
III	23	9 (31·9)
IV	7	5 (71·4)
Myometrial invasion		
Inner third	77	7 (9·1)
Middle third	60	19 (31·7)
Outer third	34	16 (47 1)
Grade		
1	117	21 (17·9)
2	37	16 (43·2)
3	17	5 (29 4)
Tumour cell type		
Endometrioid	128	28 (21·9)
Serous papillary	18	4 (22·2)
Clear cell	17	4 (23·5)
Adenosquamous	6	5 (83·3)
Squamous	2	1 (50·0)

Table 2. Cross-tabulation statistics of tumour cell type, grade, depth of myometrial invasion, stage of disease and age by lymphatic/vascular space invasion

	P value
Tumour cell type	0·014
Grade	0 007
Depth of myometrial invasion	0 0001
Stage	<0·0001
Age	0·5

Table 3. Corrected survival rates of patients with endometrial adenocarcinoma in relation to lymphatic/vascular space invasion

Lymphatic/vascular space invasion	5-year survival	10-year survival
Present	60%	42%
Absent	78%	73%

Results

The relation between lymphatic/vascular space invasion and various histopathological variables of endometrial adenocarcinoma is shown in Table 1, and the cross-tabulation correlations between these histological variables and lymphatic/vascular space invasion are shown in Table 2. Clearly, lymphatic/vascular space invasion was strongly correlated with clinical stage and depth of myometrial invasion. There was, however, a relatively poor correlation with histological type and histological grade and no correlation with the patient's age

The presence of tumour cells within lymphatic/vascular spaces had an adverse effect on survival (Table 3). The difference in survival rates at both 5 and 10 years was highly significant (P = 0·009). This disparity in patient survival was particularly striking in view of the fact that women whose tumours had invaded the lymphatic/vascular vessels had been more frequently treated with either supplementary radiotherapy, progestogens or both, than had those whose neoplasms did not show this feature (Table 4)

A multivariate regression analysis showed that lymphatic/vascular space invasion was a separate indicator of poor prognosis which was independent of stage, histological grade or depth of myometrial invasion (P = 0·018)

Discussion

In general terms invasion of lymphatic/vascular spaces by a tumour is indicative of an aggressive neoplasm which has a marked tendency to metastasize to lymph nodes and to recur locally: this has been shown to be the case for Stage 1 squamous cell carcinomas of the uterine cervix (van Nagell *et al.* 1978; Barber *et al.* 1978), for squamous carcinoma of the vulva (Parker *et al.* 1975) and for Wilms' tumours (Kumar *et al.* 1975). In the present series lymphatic/vascular space invasion by an endometrial adenocarcinoma

Table 4. Type of treatment in 171 patients with endometrial adenocarcinoma with and without lymphatic/vascular invasion

Treatment	Adenocarcinomas with lymphatic/vascular invasion *n* (%)	Adenocarcinomas without lymphatic/vascular invasion *n* (%)
Surgery alone	3 (7·1)	44 (34·1)
Surgery and radiotherapy	10 (23·8)	35 (27·1)
Surgery and progestogens	16 (38·1)	40 (31·0)
Surgery combined with radiotherapy and progestogens	13 (31·0)	10 (7·8)

also appeared to be indicative of a relatively aggressive neoplasm which was associated with a poor survival rate. It has to be emphasized that in this study poor prognosis associated with lymphatic/vascular space invasion was not restricted to tumours of high stage or with deep myometrial invasion but was also a feature of patients with Stage 1 disease and relatively superficial myometrial invasion.

Previous studies of the significance of lymphatic/vascular space invasion by endometrial adenocarcinomas have been few but have afforded results directly comparable to those found in this series. Thus Aalders *et al.* (1980) noted that the combined death and recurrence rate for cases of endometrial adenocarcinomas with lymphatic/vascular space invasion was 26·7% whereas the corresponding rate for women with tumours lacking this feature was only 9·1%. Aalders *et al.* (1984) showed subsequently that the time interval between primary treatment and the first evidence of tumour recurrence was considerably shorter for patients with demonstrable lymphatic/vascular space invasion than was the case for patients in whom this feature was absent.

Hanson *et al.* (1985) noted tumour recurrence in 44% of patients whose endometrial neoplasm was invading lymphatic/vascular spaces as opposed to a recurrence rate of only 2% in patients whose neoplasm did not invade such spaces. Furthermore, recurrences of tumours showing lymphatic/vascular space invasion tended to develop particularly in extrapelvic sites whilst recurrences associated with tumours lacking lymphatic/vascular space invasion were usually local.

More recently Geisenger *et al.* (1986) have shown a markedly reduced 5-year survival rate for patients with endometrial carcinomas whose neoplasms were invading lymphatic/vascular spaces, although the significance of this particular histological finding was not tested by multivariate regression analysis.

It is clear that the association between lymphatic/vascular space invasion and both dissemination of disease and a poor survival rate demands that this feature should be recognized as an important primary prognostic factor in endometrial adenocarcinoma. Incorporation of noting the absence or presence of this feature will, particularly in Stage 1 disease, sharpen the prognostic precision of histological examination of endometrial adenocarcinoma. The present series indicates, however, that although the finding of lymphatic/vascular space invasion may suggest that radiotherapy or chemotherapy should supplement surgical treatment there is little evidence that such therapy significantly influences the unfavourable outcome of this prognostically poor subset of endometrial adenocarcinomas.

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Received 18 November 1986
Accepted 7 January 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp 995–997

Massive subchorionic thrombohaematoma presenting as a placental tumour. Case report

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Case report

A 25-year-old Asian woman booked for her second pregnancy at 12 weeks gestation. Her first pregnancy 6 months previously had ended in miscarriage after 6 weeks of amenorrhoea.

Pregnancy was uneventful until 25 weeks gestation when the patient complained of abdominal discomfort and diminished fetal movements. On examination, her uterus was large-for-dates, giving the clinical impression of polyhydramnios. An ultrasound scan showed a normal fetus, of appropriate size and a thickened placenta with a multicystic superior margin There was no polyhydramnios Serology (TPHA, Rhesus, auto-immune disorders) was negative Measurements of human placental lactogen, human chorionic gonadotrophin and alpha-fetoprotein were all within normal limits.

Serial ultrasound scans showed normal fetal growth and a rapidly increasing placental 'tumour'. By 28 weeks, over half of the uterine cavity was filled with an homogeneous echodense mass, 18 cm in diameter at its widest point, which was beginning to compress the fetus (Fig. 1). The provisional diagnosis was that of chorioangioma, although the appearances were not typical. At this time the patient developed a normocytic, normochromic anaemia, the haemoglobin concentration falling from 11·4 g/dl to 8·7 g/dl over a period of 7 days There was no external evidence of blood loss Cardiotocographic tracings revealed loss of variability in the fetal heart rate and, following spontaneous rupture of the membranes at the end of the 28th week, the occurrence of a shallow deceleration followed by a prolonged deceleration to 60 beats/min necessitated immediate delivery. Because of the unknown nature of the 'tumour', a classical caesarean section was performed. A normal male baby weighing 1·2 kg was born, and separation of the placenta was normal.

The baby was born in poor condition with Apgar scores of 0 and 4 at 1 and 10 min respectively. The umbilical artery PO_2 was 4·46 kPa and the PCO_2 was 2·51 kPa, consistent with a pH of 7·18. The baby died at 5 days of age from the complications of prematurity and hypoxia

The placenta weighed 700 g and was circumvallate. Beneath the chorionic plate was a large laminated thrombus, 15 cm in diameter and 5 cm in depth (after fixation), typical of a subchorionic thrombohaematoma (Fig. 2). Microscopy revealed infarcted villi dispersed within the thrombus, the remaining villi showing only accelerated maturation

Discussion

Massive subchorionic thrombohaematoma (MST) is a condition of obscure aetiology (Torpin 1960), usually found in association with abortion. It has been described in association with live births (Shanklin & Scott 1975) and anomalous ultrasound appearances correlating with the condition have been described (Almond *et al.* 1983). However, there have been no reports to

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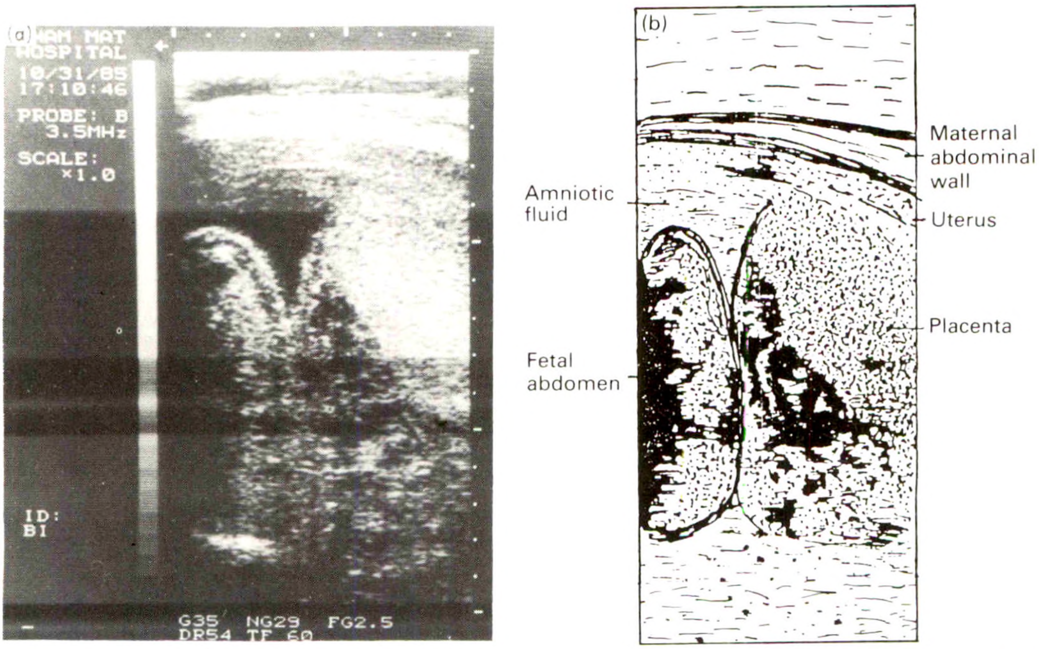

Fig. 1. (a) The ultrasound appearance at 28 weeks gestation. The placental 'tumour', seen on the right of this photograph, is compressing the fetal abdomen. (b) Diagrammatic representation of the ultrasound appearances at 28 weeks gestation.

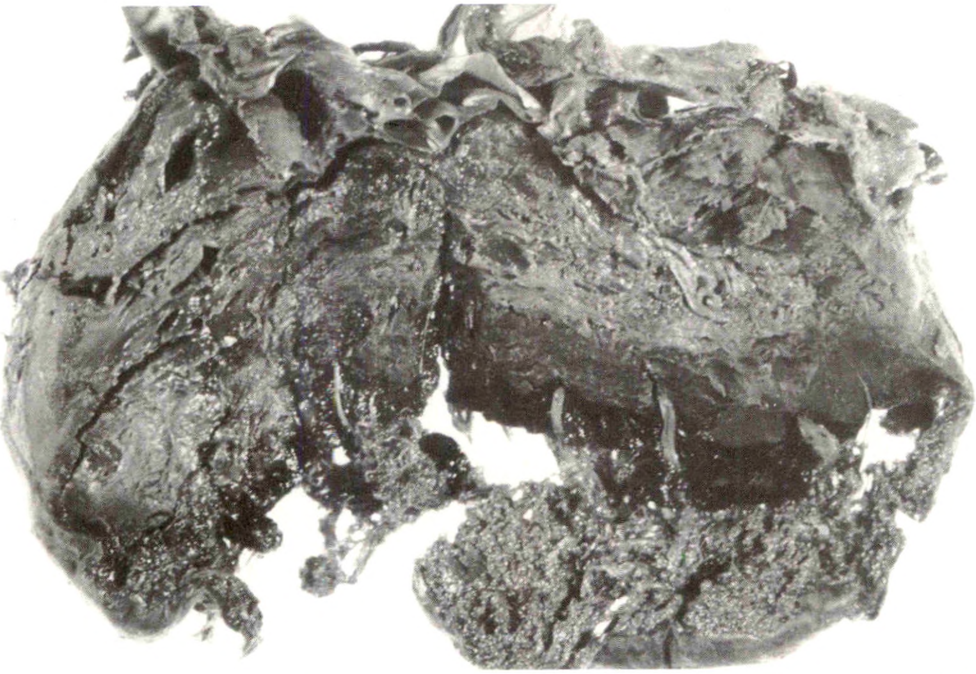

Fig. 2. Cross-sectional view of the placenta after fixation. Laminated thrombus is evident beneath the chorionic plate.

Table 1. Ultrasonic appearances of various lesions causing placental enlargement

Lesion	Ultrasonic appearance
Chorioangioma	A localized and peripherally located lesion, protruding from the surface of the placenta†
Hydatidiform mole	Manifests as echogenic tissue. Characteristic vesicles in the second trimester‡
Diabetes mellitus	Diffuse enlargement in mild/moderate diabetes, atrophic appearance in severe/juvenile diabetes*‡
Rhesus immunization	Diffuse enlargement due to oedema and hypertrophy of the villous tree‡
Severe anaemia	Diffuse enlargement of the placenta*‡
Severe infection (e g. syphilis)	

* Fox, H. 1978.
† Liang, S. T. *et al.* 1982
‡ Yiu Chiu, V. *et al.* 1982.

date describing this condition presenting as a space-occupying lesion of the placenta.

The lesion occurs when the chorionic plate is stripped away from the chorionic villous tissue by a large mass of blood clot which is principally of maternal origin. The resulting thrombohaematoma is traversed by the main cotyledonary branches of the fetal circulation. Thus it is identical to the lesion described in early pregnancy by Breus (1892) and subsequently referred to as Breus' mole.

Breus' original concept was that fetal death occurred but the placental membranes continued to grow and redundant folds of chorion became filled with blood which then clotted. Neumann (1897) first proposed that MST occurred before fetal death, and there is now a great deal of evidence to support this. Shanklin & Scott (1975) reported a retrospective study of the pathological findings in 19 000 placentas. MST was found in 10 cases, and seven of them were associated with live births. This results in an approximate prevalence of 1 in 2000. Thus, in a unit such as ours, we would expect to see one or two cases per year and this has not been our experience. It must be concluded that either the condition occurs less often than suggested, or that the condition is underdiagnosed. There is also ultrasound evidence that the formation of the thrombohaematoma occurs before any fetal compromise (Almond *et al.* 1983). It is thought that the fetus is put at increasing risk as the villous circulation is compromised by the accumulating thrombohaematoma.

The provisional diagnosis in our patient was chorioangioma, which is the commonest non-trophoblastic primary placental tumour. However, the typical features of this tumour were absent (Table 1). Other causes of an enlarged placenta were also considered.

The diagnosis of MST raises the problem of management. Until the fetus shows evidence of distress, the presence of MST would not appear to be an indication for the termination of the pregnancy nor for early delivery. However, MST must be considered to be an indication for regular fetal cardiotocography, and any signs of deterioration must be taken as an indication for immediate delivery. After delivery, it is essential that the placenta is examined carefully.

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Received 8 September 1986
Accepted 6 January 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol. 94, pp. 998–999

Pituitary failure from Sheehan's syndrome in the puerperium. Two case reports

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Case reports

Patient no. 1

This 34-year-old woman was admitted at term in her fourth pregnancy. She had an emergency caesarean section for fetal distress and bled heavily from a uterine tear. She was hypotensive for several days postpartum with supine systolic blood pressure rarely above 80 mmHg.

Postoperatively the patient was listless and reluctant to eat. She showed little interest in her baby and was thought to be depressed. She did not lactate. She continued to be very lethargic on discharge home where she was carefully followed by her family doctor who suspected hypothyroidism. The results of this investigation revealed a low T_4 of 11 nmol/l with normal TSH of 2·3 mU/l suggesting secondary hypothyroidism. On admission she was found to be pale with a dry skin. Supine blood pressure was 78/50 mmHg. A combined pituitary function test performed 33 days postpartum demonstrated panhypopituitarism. Replacement therapy with thyroxine and hydrocortisone resulted in a rapid improvement.

Patient no. 2

This 34-year-old patient was admitted at term in her third pregnancy. Following an apparently normal vaginal delivery she became shocked and uterine rupture with massive blood loss was diagnosed at laparotomy.

Recovery was slow and complicated by disturbed visual spatial perception attributed to occipito-parietal (watershed) ischaemia. The patient failed to lactate and it was suggested to her that Sheehan's syndrome would probably develop with the passing years However, because it was felt that no abrupt change in her pituitary function would occur it was decided to refer her for endocrine investigation when she had recovered from the events surrounding the delivery. On discharge home at 14 days postpartum she was still lacking in energy and feeling generally unwell. Her family doctor was concerned about her lack of progress and persistent hypotension and she was referred for urgent endocrine investigations. The patient was readmitted 23 days postpartum when she was clearly very ill. She was very pale with a cold dry skin, a rectal temperature of 34·2°C and a supine blood pressure of 80/60 mmHg. She was very sleepy and difficult to rouse. Investigations on the day of admission demonstrated panhypopituitarism. During the pituitary function tests she became severely hypoglycaemic and required intravenous hydrocortisone and glucose. Following introduction of replacement therapy with thyroxine and hydrocortisone she made a very rapid recovery.

Discussion

Acute ischaemic necrosis of the pituitary associated with blood loss during delivery was first described by Sheehan (1937) and there have been many subsequent reports. While the haemorrhage and hypotension are usually severe, Sheehan's syndrome has been reported after apparently modest blood loss (Hall 1962). A failure of lactation is an early indication that pituitary function has been impaired but, typic-

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ally, the additional clinical features of pituitary insufficiency appear much later (Frohman 1985). The original description by Sheehan (1937) commented on the possibility of profound pituitary failure in the puerperium but this fact does not feature in contemporary textbooks of medicine, probably because Sheehan's syndrome itself is becoming less common in developed countries.

The particular vulnerability of the pituitary to circulatory shock is thought to relate in part to its considerable increase in size and vascularity during pregnancy. In addition, the vasoconstrictive effects of hypoxia may be increased by oestrogen resulting in spasm of the hypophyseal vessels. Although classically Sheehan's syndrome is preceded by obvious and profound blood loss, the first case report demonstrates that only transient and apparently modest haemorrhage can also lead to acute ischaemic necrosis of the pituitary.

Sheehan's syndrome can occur with widely differing severity. In one series only half of 25 women with Sheehan's syndrome failed to lactate or went on to develop amenorrhoea (Drury & Keelan 1966). There have been several reports of subsequent pregnancies in women with Sheehan's syndrome (Grimes & Brooks 1980) and indeed the condition may first present as hypoglycaemia during a later pregnancy (Smallridge *et al.* 1980). The more usual presentation, however, is of sequential loss of anterior pituitary hormonal function long after the index pregnancy.

The two patients presented here demonstrate that, at the other end of the severity spectrum, Sheehan's syndrome can present acutely in the puerperium with potentially lethal pituitary failure. Apathy is usually the first manifestation but this is often ascribed to postnatal depression. The condition of the patient will rapidly and progressively worsen and, as in our two patients, profound illness will supervene some 3–4 weeks after the delivery. Failure to identify the diagnosis at this stage can clearly be life-threatening. Indeed, Sheehan (1937) described massive pituitary necrosis in women who died in the puerperium following major haemorrhage.

In our second patient the failure of lactation was correctly ascribed to Sheehan's syndrome but, because of the widely held belief that the full syndrome does not develop for many months or years, it was decided to defer endocrine investigations until her general condition had improved. Any patient in whom Sheehan's syndrome is suspected should be investigated endocrinologically before leaving hospital.

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Received 1 September 1986
Accepted 5 May 1987

British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp. 1000–1002

SHORT COMMUNICATIONS

Allogeneic activation is increased during pregnancy. A risk factor in HIV infection?

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The question has been raised whether allogeneic stimulation or immunosuppression might act as one of the co-factors that can exacerbate HIV disease during pregnancy (Pinching & Jeffries 1985; Peckham *et al.* 1987). We investigated urinary neopterin levels in a 26-year-old woman during 14 weeks of her pregnancy using standard HPLC-techniques (Hausen *et al.* 1982). The patient had a history of parenteral drug abuse for 10 years and anti-HIV-seropositivity (Abbott-ELISA confirmed by Western blot and immunofluorescence test) was known for 1 year. The woman presented without any AIDS-related signs or symptoms during the whole observation period. She was first seen at 16 weeks gestation when she had a CD4$^+$/CD8$^+$ T-cell subset ratio of 0·17 and her urinary neopterin was highly elevated compared both with healthy controls and uncomplicated pregnancies (Fig. 1). Although the patient admitted to the intermittent use of drugs, the pregnancy was normal until week 31 except for a 5-week retardation of fetal growth diagnosed by sonography. In week 31, intrauterine death was diagnosed and delivery was induced. Urinary neopterin levels were highly elevated throughout the pregnancy (Fig. 1) with a mean value of 752 μmol neopterin/mol creatinine which was 177% of the already high level of 425 μmol neopterin/mol creatinine present before her pregnancy. Urinary neopterin is elevated in almost all individuals infected with HIV (Wachter *et al.* 1986). After the delivery, neopterin decreased to a level of about 550. Our patient remained free from AIDS-related symptoms for a further 10 months until now. The increase of neopterin excretion found indicates an additional activation of the T-cell/macrophage axis (Huber *et al.* 1984; Nathan 1986) during pregnancy. Neopterin levels are also higher in normal pregnancy compared with non-pregnant controls (Bichler *et al.* 1983) but the concentrations in our HIV-infected patient rose dramatically.

Since activated T-cells are detectable in a high

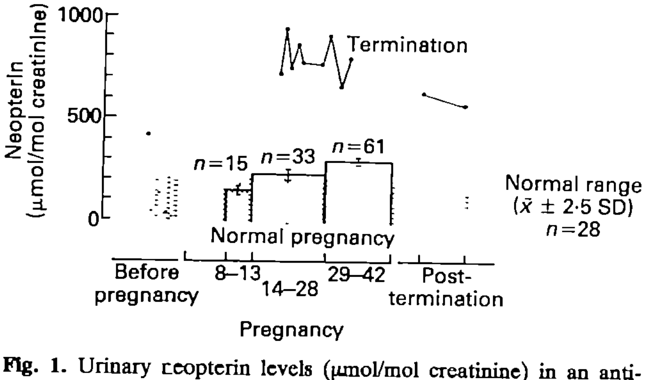

Fig. 1. Urinary neopterin levels (μmol/mol creatinine) in an anti-HIV-ab seropositive drug addict before, during and after pregnancy compared with normal pregnancy (bars, mean ± SE) and healthy women (dotted area).

proportion of all groups at risk of AIDS, and in agreement with the in-vitro situation, in our opinion activation of T-cells represents the crucial event which accounts for progressive HIV expression (Wachter *et al.* 1986; Fuchs *et al.* 1987). Neopterin levels which were found in our HIV-seropositive patient are in a range such as is found in acute pulmonary tuberculosis (Fuchs *et al* 1984). Thus, pregnancy induces a higher degree of T-cell activation in HIV-seropositives and we conclude that T-cell activation may account for the observation that pregnancy induces worsening of HIV infection.

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Received 2 June 1987
Accepted 29 June 1987

Association between prostaglandin E_2 and placental abruption

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Many patients needing induction of labour have unfavourable cervices and prostaglandins have been used both to ripen the cervix and speed delivery.

We have used vaginal pessaries (Prostin E_2, Upjohn) containing 3 mg of prostaglandin E_2 (PGE_2) in patients for induction of labour if the gestational age was >36 weeks and the Bishop score was <7 (Bishop 1964). These patients had a non-stress test in the evening, and the pessary was given if the test was reactive (Baskett *et al.* 1981). The membranes were ruptured next morning if the cervix was favourable for induction, and oxytocin was given if contractions were not established after that. The regimen was repeated 24 h later if the Bishop score remained <7 on the following day.

Table 1. Association between placental abruption and prostaglandin E_2 (PGE_2) ripening of the cervix after 36 weeks gestation

	Induction of labour			
Placental abruption	PGE_2	No PGE_2	No induction	Total
Present	7 (0·78%)	1 (0·06%)	15 (0·19%)	23
Absent	893	1603	7692	10 188
Total	900	1604	7707	10 211

We have noticed an apparent increase in small intrapartum haemorrhage and the finding of retroplacental clots after delivery of the placenta, and considered the possibility of an association between early placental separation and the use of prostaglandin. We therefore conducted a retrospective survey of our patients

The survey included 10 211 patients who were delivered in the period May 1984 to July 1986, and 900 of them had received prostaglandin. Placental abruption was defined as the presence of a retroplacental blood clot when the placenta was examined after delivery or during caesarean section All the placentas were examined by two registered midwives or medical staff.

There were 23 patients with placental abruption, seven of these had received prostaglandin (Table 1), making a frequency of 0·78%. The rate of placental abruption in patients induced without PGE_2 was 0·06%. This difference was statistically significant (χ^2 14·44, $P<0{\cdot}001$).

In the seven patients with placental abruption associated with prostaglandin, the indications for induction were pregnancy beyond 41 weeks (3), diastolic blood pressure 90–100 mmHg near term (1), proteinuric pre-eclampsia near term (1), suspected intrauterine growth retardation (1), and one episode of antepartum haemorrhage of unknown origin (1). Apart from the last patient, none had antepartum haemorrhage before induction. The association between placental abruption and prostaglandin remains statistically significant even if the last patient is excluded from analysis (χ^2 10·44, $P<0{\cdot}01$). Six patients received only one dose of PGE_2 (3 mg) The patient with growth retardation received two doses of 3 mg each 24 h apart

Five babies were born by caesarean section for fetal distress evident by abnormal fetal heart tracing. The other two babies were born vaginally. Of the five babies born by caesarean section, two required admission to the neonatal intensive care unit because of birth asphyxia. They were both discharged in good condition.

We believe that an association between prostaglandin and placental abruption has not been reported previously. This may be due to the very low frequency of placental abruption, so that an increase is only noticeable in a large series.

It is possible that our result is merely a statistical accident, but the implications are such that a prospective study with a large series seems worthwhile. If this result can be replicated, it may explain the occasional occurrence of sudden fetal death (Quinn & Murphy 1981; Stewart & Calder 1981), and stresses the need for close monitoring of patients after prostaglandin insertion

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Received 11 November 1986
Accepted 17 February 1987

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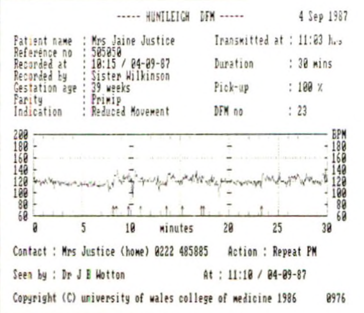
THE CASE
FOR FETAL MONITORING
BY TELEPHONE

Huntleigh DFM allows antepartum monitoring to be carried out at the patients home or healthcentre...



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----- HUNTLEIGH  DFM -----                 4 Sep 1987

Patient name   : Mrs Jaine Justice     Transmitted at : 11:03 hrs
Reference no   : 505050
Recorded at    : 10:15 / 04-09-87      Duration       : 30 mins
Recorded by    : Sister Wilkinson
Gestation age  : 39 weeks              Pick-up        : 100 %
Parity         : Primip
Indication     : Reduced Movement      DFM no         : 23
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200
180
160
140
120
100
80
60
BPM
0
5
10
minutes
20
25
30

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Contact : Mrs Justice (home) 0222 485885   Action : Repeat PM

Seen by : Dr J B Wotton                    At : 11:10 / 04-09-87

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...and transmitted to hospital in 45 seconds for expert interpretation.

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British Journal of Obstetrics and Gynaecology
October 1987, Vol. 94, pp. 1003–1004

CORRESPONDENCE

Does conception before marriage matter?

Dear Sir,

Using data collected in the UK in 1970, Golding *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 38–43] showed that compared with infants conceived within marriage, those conceived before marriage were at an increased risk because of maternal youth, primiparity and maternal health behaviour and this group had a slight excess of preterm births when the other risk factors were taken into account.

We want to give further information on this risk factor with more recent data from France where fertility characteristics (fertility rate and proportion of illegitimate births) and perinatal mortality are very similar to those observed in the United Kingdom (EUROSTAT 1986). Data were derived from a national sample of births in 1981 (Rumeau-Rouquette *et al.* 1984). Premarital conception was defined as the birth of an infant <7 months after marriage and in 1981 6·4% of the married women conceived before marriage. The following results were restricted to primiparous women because they represented 88% of the premarital conceptions and their family and social situation is very specific and homogeneous.

As was shown in the UK, demographic and social characteristics of the women varied markedly with their marital status at conception; in the premarital conception group 26·9% were teenagers compared with 6·3% in the other group ($P<0{\cdot}001$); moreover 20·1% of the premarital conception group left school without any diploma compared with 14·1% of the other group ($P<0{\cdot}05$).

The proportion of low birthweight (≤2500 g) did not differ significantly between the two groups but 8·2% of the premarital conception group had a preterm delivery compared with 4·5% of the other group ($P<0{\cdot}01$). Premarital conception was still significantly associated with preterm delivery when maternal age or educational level was taken into account.

These results show that in 1981 premarital conception was still a risk factor. Nevertheless there have been great changes in marriage and fertility recently in France and in the UK. The rate of marriage and the proportion of premarital conceptions have decreased dramatically while the proportion of illegitimate births has become more and more important. in 1984, there were 16% of illegitimate births in France and 17% in the United Kingdom In these two countries the risk of adverse pregnancy outcome is greater among unmarried women than among women who had a premarital conception. Golding *et al.* (1986) showed that in 1970 in the United Kingdom 9·8% of unmarried women (single or once married) had a preterm delivery compared with 7·3% of the premarital conception group ($P<0{\cdot}01$). In France in 1981 these rates were 11·0% among unmarried women not cohabiting with the child's father, 8·4% among unmarried women cohabiting and 8·2% among married women (primiparae and multiparae) who had a premarital conception (Zuber 1987). Although the difference between the first group and the other two is not significant, it seems that unmarried women living alone represent the least favoured group and that unmarried women cohabiting as well as women with premarital conception are in an intermediate situation between married women and women living alone.

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Zuber, M. C. & Blondel, B. (1987) Statut matrimonial, cohabitation et grossesse. Evolution des aspects sociaux et médicaux des naissances hors mariage *Population* (in press)

Book review by D. G. Altman: The Derivation and Exploitation of Empirical Birthweight Standards

Dear Sir,

In his review of our book [*Br J Obstet Gynaecol* (1987) **94,** 379–381] on the derivation of birthweight standards, Douglas Altman rightly drew attention to the very small numbers in groups below 36 weeks. Whilst we would expect mean birthweight to increase even at early gestations in larger samples, a central argument of our book is that there is no reason to expect that mean birthweight at different gestational ages should be on a smooth curve. The issue is not the feasibility of fitting a statistical model—which is always possible—but what it means and whether it is appropriate

In a clinical context, the assessment of light-for-dates or heavy-for-dates may have implications for treatment. The presentation of a smoothed set of standards would seem to promote consistent criteria for interventions; but there is no basis for any one statistical adjustment rather than another. The presentation of raw data not only provides the clinician with the option of smoothing; it draws attention to the dangers of such an exercise; and, more importantly suggests that considerable caution should be exercised in the use of any set of standards for intervention. As Thomson (1983) says 'centiles should not be interpreted as implying different levels of risk in themselves unless there is external evidence showing that such differential risks do in fact exist'. For the researchers, the utility of a set of adjustments depends on their transparency. The assessment of deviations from a norm is rendered opaque if the norm has been derived by smoothing a population with unknown characteristics and distribution of birthweights.

Hence our preference for empirically derived, locally based standards. Indeed, as we emphasized several times, the intention was to illustrate a procedure for their derivation rather than to promote a new set of standards. Following this approach, we are now preparing a paper including standards for clinical use based on a complete geographical population where these issues are also addressed.

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Carr-Hill, R & Pritchard, C. (1985) *The Derivation and Exploitation of Empirical Birthweight Standards,* Macmillan Press, Basingstoke.

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British Journal of Obstetrics and Gynaecology
October 1987, Vol 94, pp 1005–1008

BOOK REVIEWS

The Human Placenta: Clinical Perspectives edited by J. Patrick Lavery. Aspen Publishers Inc., Rockville, Maryland, 1987, 288 pages with figures and tables, $59.00

This book aims to emphasize the critical role played by the placenta in the outcome of pregnancy and to present the placenta in its clinical perspective. It is directed at all those involved in the obstetrical care of women, this rather wide targeted potential readership including not only obstetricians but also midwives, labour room attendants and delivery room nurses.

Virtually all aspects of the placenta are considered, though the arrangement of the chapters is curiously illogical. There are good contributions on placental development, twin placentation, placental infections and the immunological aspects of the placenta as a graft: I doubt, however, if all the intended readers will have the necessary background of immunological knowledge required to appreciate the excellence of this last chapter.

Other contributions are less satisfactory and I found those dealing with placental physiology unduly skimpy. The chapter on placental endocrinology will leave no-one with a clear concept of the placenta as an endocrine organ: further, the authors of this chapter commit the truly dreadful solecism of equating PAPP-A with SP1. A chapter on placental pathology is somewhat uncritical, lacks a coherent philosophical approach to the whole topic of the pathology of this organ and is written in unacceptably poor English: such phrases as 'the importance of placental exam is clearly illustrated' represent a new nadir of medical literacy. The author of the chapter on placental function tests appears to cling to the now discredited belief that fetal complications are commonly due to placental malfunction and I find it difficult to accept that fetal heart rate monitoring is truly a test of placental function. Some chapters, such as those dealing with the third stage of labour, are almost entirely concerned with clinical management and sit uneasily cheek by jowl with the more scientific contributions.

A good opening chapter on the history of placental studies is followed by a truly amazing account of 'the cultural anthropology of the placenta'. I will probably be classed as uncaring, narrow minded and bigoted if I dismiss this chapter as pseudointellectual twaddle but I am afraid that is exactly what it is. I was, however, dismayed to discover that one of my long cherished projects, namely to write a 'Placenta Cook Book' for those women wishing to eat their placenta, has been pre-empted and that recipes are now available for such delicacies as placenta pizza.

The aim of this book is praiseworthy but I do not feel that I can confidently recommend it. It is written at too many different levels, lacks a clearly defined and coherent approach and is too diffuse in its aims. I feel that a very much better book could have been written by just two or three authors.

H. Fox

Prospective Studies on Children with Sex Chromosome Aneuploidy (March of Dimes Birth Defects Foundation. Birth Defect Original Article Series, Vol. 22 No. 3 1986) edited by Shirley G. Ratcliffe & Natalie Paul. Alan R. Liss Inc., New York, 1986, 328 pages with figures and tables, £63.00

This volume contains a collection of papers representing the fourth workshop for investigators carrying out prospective longitudinal studies on children with sex chromosome abnormalities, sponsored by the March of Dimes Birth Defects Foundation. The sex chromosome abnormalities were XXY (Klinefelter's syndrome), XYY, XXX, XO (Turner syndrome), and to a limited extent chromosome mosaics. The cases in the study came from newborn cytogenetic surveys commenced in the mid 1960s at seven centres around the world; 307 children in all were included.

There is a wealth of interesting psychological and clinical data in this book, that will be of value to anyone advising parents about the long-term effects of such a chromosome abnormality, particularly if it is picked up by prenatal screening. The greatest effect of a sex chromosome abnormality on metal development appears to be in 47,XXX females, where intelligence is on average lowered by 15–20 points. In 47,XXY males, verbal IQ seems to be lowered by 10 points but performance IQ is no different from controls; 47,XYY males and 45,XO females showed no significant difference in IQ from controls.

On the limited data available, it appears that 47,XYY males may not have a greatly increased tendency to psychopathic behaviour or educational and behavioural problems. In a study of Danish XYY males, ascertained because of height in the top 15% of the population distribution, Theilgaard did not find any difference in psychotic or depressive tendencies between XYY and XXY males.

This book is well worth dipping into, particularly the summary chapter at the end by Netley, but at £63.00 for 328 pages it is definitely a volume to be borrowed and not bought.

R. M. Winter

American Journal of Kidney Diseases Vol. IX, No. 4, 1987, Symposium on Renal Function and Disease in Pregnancy. An International Symposium edited by Marshall D. Lindheimer & Christine Baylis. Grune & Stratton, Orlando, 1987, 280 pages with figures and tables, $15.00

Almost universal complaints of the book reviewer are that the book costs too much and that it is already out of date. For that reason it is occasionally appropriate to draw attention in these columns to an example of publishing which avoids both those problems.

In September 1986, an International Symposium was held in Chicago on Renal Function and Disease in Pregnancy to summarize present knowledge, to derive guidelines for the clinical management of pregnant women with renal problems, and to suggest areas which particularly require research effort.

The results were published in this April 1987 issue of the American Journal of Kidney Diseases.

There are excellent, comprehensive and totally up-to-date summaries of all physiological aspects, both in man and animals by active research workers; they present not merely the established facts but intellectually stimulating ideas and hypotheses.

Pre-eclampsia, its often complex clinical presentation, its disputed pathology and its treatment, is presented in terms of selected items along its growing edge, a provocative stimulus to any reader who might have felt that the subject is bogged-down.

Finally, there is an excellent up-to-the-minute collection of papers on a variety of renal diseases in pregnancy including the problems raised by dialysis and renal transplantation.

All obstetricians should have access to this information and anyone seeking a book on renal disease in pregnancy would be well advised to look at this journal issue first.

F. E. Hytten

Advances in Perinatal Medicine Vol. 5 edited by Aubrey Milunsky, Emmanuel A. Friedman & Louis Gluck. Plenum Medical Book Company, New York, London, 1986, $49.50

For today's clinicians in-depth reviews are an old-fashioned luxury—redolent, like spats and chauffeurs, of a gracious yesteryear. Nowadays most doctors keep up to date with thousand-word editorials while a few enthusiasts—examination candidates, for instance—are willing to tackle eight-page reviews. Much as I enjoy this trend to conciseness, there is still a place for the more comprehensive article, provided authors can be found who are able to sculpt a readable text from a drawerful of references. The 280 pages of Volume 5 of *Advances in Perinatal Medicine* contain only half-a-dozen articles and the contributors are mainly from the United States, though one chapter—on transplacental toxicity of environmental chemicals—comes from Finland The subjects cover both obstetrics and neonatology. Chapter 1 describes how intrauterine growth retardation can be treated by giving nutritional supplements direct to the fetus· according to Dr Charlton the therapy appears promising but seems better at preventing the progression of early growth retardation than at rescuing the severely affected fetus. Chapter 6 is a relatively brief discussion of Chlamydial infection and pregnancy outcome. Haemodynamics is now an up-and-coming subject in the world of obstetric research, but the review in this volume confines itself to the neonatal aspects of hyperviscosity and polycythaemia. For obstetricians the business-like chapter on the use of psychoactive substances during pregnancy is particularly useful, summarizing the effects of a range of agents from cigarette smoking through marijuana to diazepam. The chapter on drugs given in labour occasionally falls into the trap of giving chronological lists of the results of research papers rather than marshalling its facts more readably, but the authors compensate for this with regular summaries. The language throughout is clear and the only lapse of style comes—surprisingly—in the editors' own preface. However, having shown such flair in eliciting good writing as well as good science from their contributors, they can be forgiven a little grandiloquence.

J. O. Drife

Diagnosis and Management of the Fetus and Neonate at Risk. A Guide for Team Care. Fifth edition by Martin L. Pernoll, Gerda L. Benda & S. Goram Babson. The C. V. Mosby Company, St Louis, 1986, 364 pages with figures and tables, £33.50

This book has clearly proved very popular as it has run to five editions in the last 20 years, and aims to summarize all aspects of diagnosis and management of the compromised fetus or newborn as a continuum. It is a handbook for the perinatologist if such a being truly exists. It sensibly begins by emphasizing that risks to babies begin at, or even before, their conception but that such at-risk infants can be identified early in the antenatal period, if appropriate care is taken. The book details standard US antenatal practice and how this should be varied if problems are identified. The style of the book varies from almost chatty prose to pages of rather indigestible lists of risk factors and causes. Traditional methods of assessing the fetus *in utero* are covered in some detail but remarkably little information is given about the role and use of ultrasound and chorionic villus sampling. The delivery of the at-risk fetus again is covered by long lists of risk associations during delivery and some other lists covering intrapartum techniques such as analgesia and caesarean section. The chapters on resuscitation and stabilization of the newborn and immediate neonatal assessment are very brief but concise. The last two thirds of the book are about intensive care of sick newborn infants but relate the problems encountered to their obstetric antecedents. This is perhaps the book's strongest point and it aims to emphasize the continuity of the problems besetting these infants and the need for co-operation between obstetrician and paediatrician throughout.

An enormous amount of information is packed into these pages but again its presentation in list form makes it rather indigestible. A number of appendices give further lists of what to take on neonatal emergency transport (and remind you not to forget a torch and your pen), examples of record sheets and a very brief one-page appendix on drug dosages in the newborn. This book would be of most use to those studying fetal medicine options in postgraduate medical courses in obstetrics, and the book's emphasis on continuation of care and team management is certainly to be encouraged. However, in trying to cover such a wide field much of the information this book contains is inevitably very compressed and just a little dated. Candidates might well do better with a standard modern obstetric text and a small handbook of neonatal intensive care.

Richard Cooke

Semen Analysis: A Practical Guide by Anne Jequier & Joan P. Crich. Blackwell Scientific Publications, Oxford, 155 pages with figures and tables, £25.00

It has been claimed that semenalysis has done more harm to the cause of infertility than any other three factors put together! Some of this harm can be ascribed to poor laboratory technique but rather more to the misinterpretation of results. The authors have set out to address the first of these difficulties, but express the hope that clinicians involved in treating infertile couples will also find the work valuable. The book is a well-written and concise account of the complete range of techniques that might be used in a laboratory aiming to provide a comprehensive investigative service for male infertility. The title suggests that only those items found on a standard semen analysis report are considered, but the scope is much more extensive including such things as anti-sperm antibody tests, postcoital tests, mucus penetration tests, cryo preservation of semen, as well as sections on the anatomy and physiology of the male genital tract. The terms used in semenology (and often misused by clinicians) are clearly defined.

This book will be a useful reference manual for anyone working in a pathology laboratory undertaking semen analysis, or embarking on clinical research using such techniques. However, from the clinician's point of view, its value is limited by the lack of discussion of normal values and the relevance of departures from the norm. This seems particularly sad as the authors have the expertise to have given sound advice on the use of these tests to avoid future generations of men with sperm densities of 18 million/ml being told that they are sterile.

David Joyce

Books received some of which may be reviewed at a later date

Neonatal Medicine edited by Leo Stern & Paul Vert. Masson Publishing USA, Inc., New York, 1987, 1215 pages with figures and tables, £81.50

Fetal and Neonatal Pathology edited by Jean W Keeling. Springer-Verlag, London. Heidelberg, 1987, 590 pages with figures and tables, £99.00

Jeffcoates's Principles of Gynaecology Fifth Edition edited by V. R. Tindall. Butterworths, London, 1987, 722 pages with figures and tables, £45.00

Immunoregulation and Fetal Survival edited by T. J. Gill III & Thomas G. Wegmann with E. Nisbet-Brown. Oxford University Press, Oxford, 1987, 324 pages with figures and tables, £42.00

Hematologic Problems in Pregnancy edited by David Z. Kitay. Medical Economics Books, New Jersey, 1987, 423 pages with figures and tables, $39.95

Labor and Delivery: Impact on Offspring by E. A. Friedman & R. K. Neff. PSG Publishing Company, Inc., Massachusetts, 1987, 523 pages with figures and tables, £49.50

British Medical Bulletin: Recurrent and Chronic Psychosis, Vol. 43, No. 3, July 1987 edited by T. J. Crow. Published for the British Council by Churchill Livingstone, Edinburgh, 479–733 pages, subscription rates £50.00 (UK) or £55.00/$99.00 (overseas), single copies £20.00 (UK) or £21.25/$40.00 (overseas)

Genetic Risk, Risk Perception and Decision Making (March of Dimes Birth Defects Foundation. Original Articles Series Vol. 23 No. 2 1987) edited by G. Evers-Kiebooms, J. J. Cassiman, H. van den Berghe & G. d'Ydewalle. Alan R. Liss, Inc., New York, 333 pages with figures and tables, £63.85

Medical and Experimental Mammalian Genetics: A Perspective (March of Dimes Birth Defects Foundation. Original Articles Series Vol. 23 No. 3 1987) edited by V. A. McKusick, T. H Roderick, J. Mori & N. W. Paul. Alan R. Liss, Inc., New York, 358 pages with figures and tables, £63.40

Comprehensive Gynecology by W. Droegemueller, A. L. Herbst, D. R. Mishell Jr & M. A. Stenchever. The C. V. Mosby Company, St Louis, 1987, 1149 pages with figures and tables, £49.00

Synopsis of Gynecologic Oncology Third Edition edited by C Paul Morrow & D. E Townsend. John Wiley & Sons, New York, Chichester, 1987, 584 pages with figures and tables, £41 30

Endometriosis edited by Emery A. Wilson. Alan R Liss, Inc., New York, 1987, 248 pages with figures and tables, £24.00

Endoscopic Laser Surgery Handbook (Science and Practice of Surgery Series/10) edited by S. M Shapshay. Marcel Dekker, Inc., New York, 1987, 520 pages with figures and tables, $150.00

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution, major changes will be agreed with the author(s)

Presentation of manuscripts

Two copies of the manuscript and illustrations should be sent Manuscripts should be typed double spaced on one side of the paper, with wide margins The names of author(s) and their appointment(s) and addresses at the time of preparation of the manuscript should be given. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss

Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part Two further sub-divisions, with appropriately less significant headings, can be used, the third order heading runs on with text at a paragraph opening Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables. The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s)

Case reports and short communications do not require a summary or introduction Short communications should not exceed 600 words and contain no more than one table or figure

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin Both are numbered with arabic numerals Colour illustrations are allowable only in special circumstances and the author will be expected to meet the cost of reproduction

Figures should be marked on the back (light in pencil) with the name(s) of the author(s), the figure number, and the top indicated Each should have a descriptive legend typed on a sheet separate from the figure Photographs should be unmounted glossy bromide prints of good contrast

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc Tables are not included in this classification and should not be submitted as photographs Original X-ray films should not be sent—glossy prints must be submitted

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column)

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself

The identity of patients in illustrations should be concealed by masking the face or eyes, or written permission for publication from the patient or the parent or guardian must be supplied

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg) If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors Standard abbreviations, without punctuation, are used *Units, Symbols and Abbreviations* (1977) published by the Royal Society of Medicine provides a useful guide Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text

Statistics

Authors should describe clearly the design of their investigation and the source of the data All statistical methods should be specified so that it is clear which was used where Papers omitting this information may be returned without review The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else

Some points of detail to note are

(1) It is not acceptable to present the results of a statistical analysis solely by a P value—actual results such as means or proportions should always be given, along with the test statistic
(2) The use of confidence intervals is encouraged
(3) The symbol ± should not be used when presenting SE or SD Presentation such as 'the mean was 14·2 (SD 3 2) mg' is preferred
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
(5) Unusual methods of analysis should be described and/or referenced

Authors are referred to the general statistical guidelines of Altman *et al* (1983) for advice about the presentation and interpretation of the statistical aspects of their research

> Altman, D G , Gore, S M , Gardner, M J. & Pocock, S J (1983) Statistical guidelines for contributors to medical journals *Br Med J* **286,** 1489–1493

Human experiments

Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work The editors reserve the right to reject papers if they consider the ethical justification to be questionable

References

In the text, use the name of the author(s) followed by their date of publication, where there are two authors use the form Smith & Brown 1972; where there are more than two authors use Robinson *et al.* 1979

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers In the case of books the order is Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers Where appropriate, the chapter title and the names of the editors should be given

References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references Examples of the style to be used are given below·

> Trudinger, B J , Lewis, P J & Petit, B (1979) Fetal breathing in intrauterine growth retardation *Br J Obstet Gynaecol* **86,** 432-436
>
> Hytten, F E & Leitch, I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p 26

Proofs and offprints

Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent Only essential corrections can be accepted; more extensive alterations, which may delay publication, will be charged to the author Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed card sent with the proofs

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BLACKWELL SCIENTIFIC PUBLICATIONS
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Printed in Great Britain by Headley Brothers Ltd The Invicta Press Ashford Kent and London

Volume 94, Number 11, November 1987

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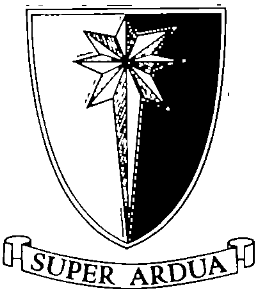
British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten



Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications
BJOGAS 94(11) 1009–1120 1987 ISSN 0306-5456

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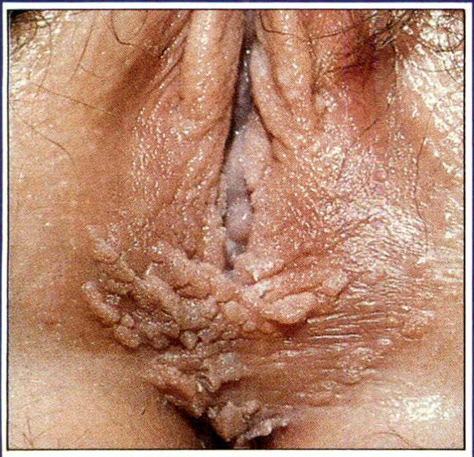

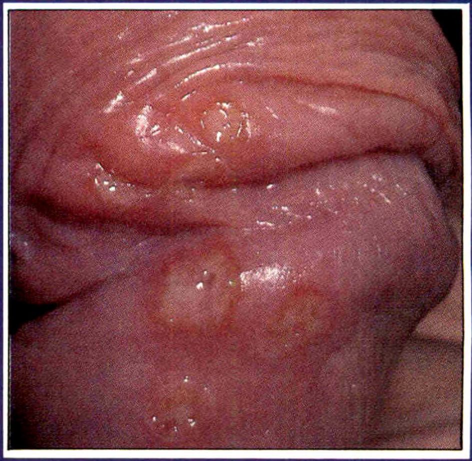

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, **301,** 677. 2. Richardson,J.A. & Dixon,G., *Brit.Med.J.*, 1976, **1,**
. 3. Chen.J.K. & Elder,M.G., *Obstet.Gynecol.*, 1983, **62,** 339.
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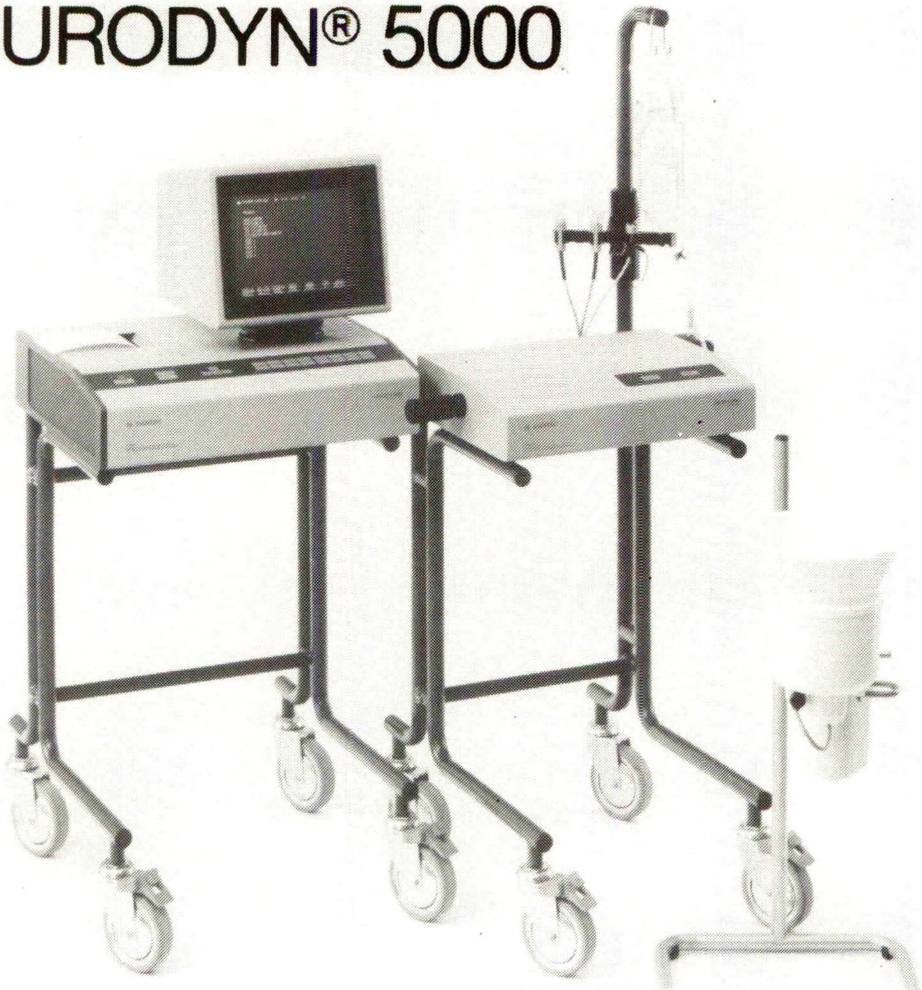

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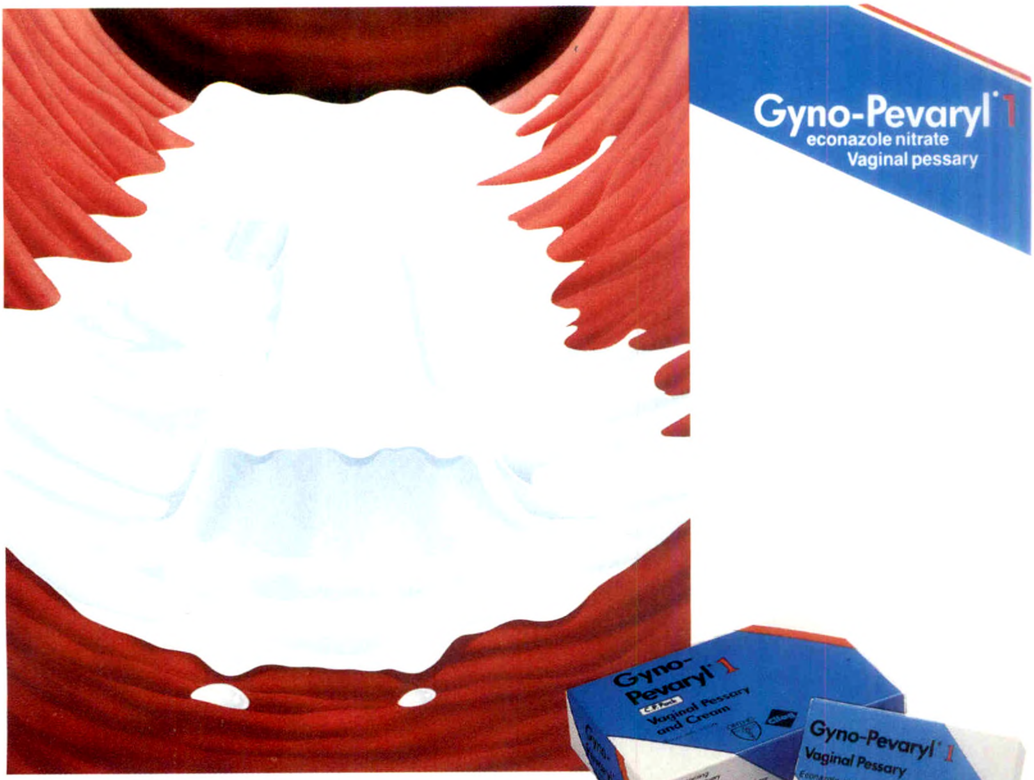

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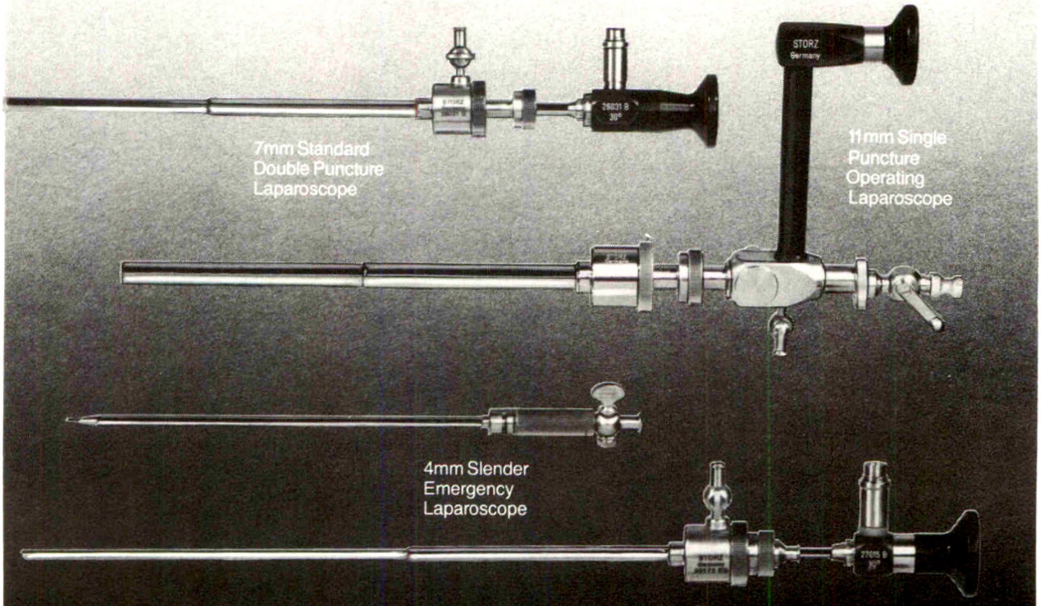

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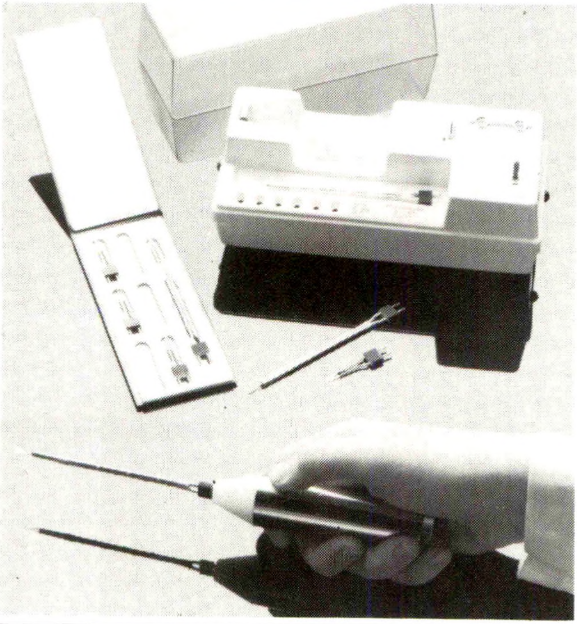

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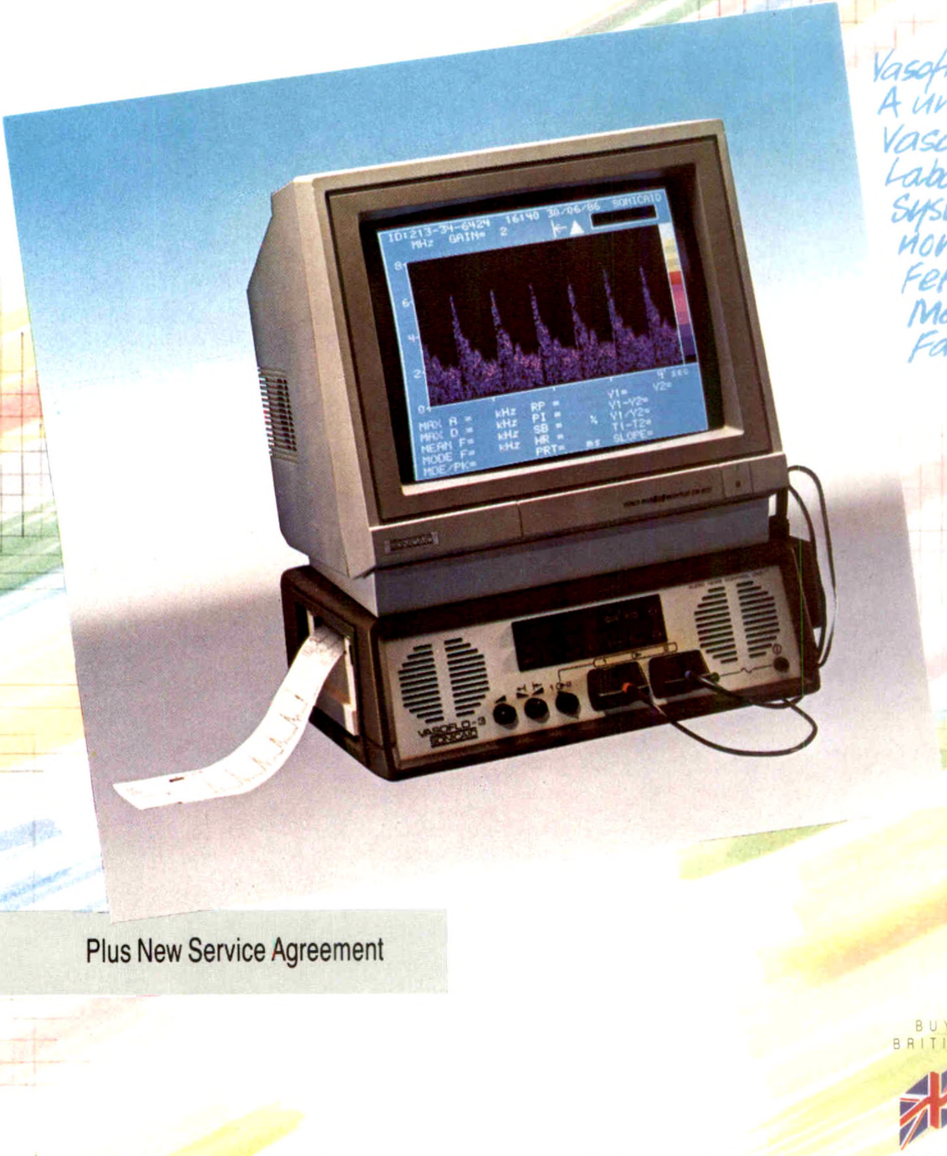

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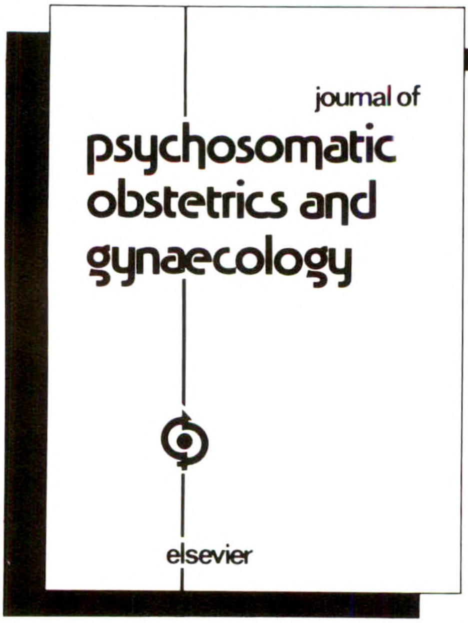

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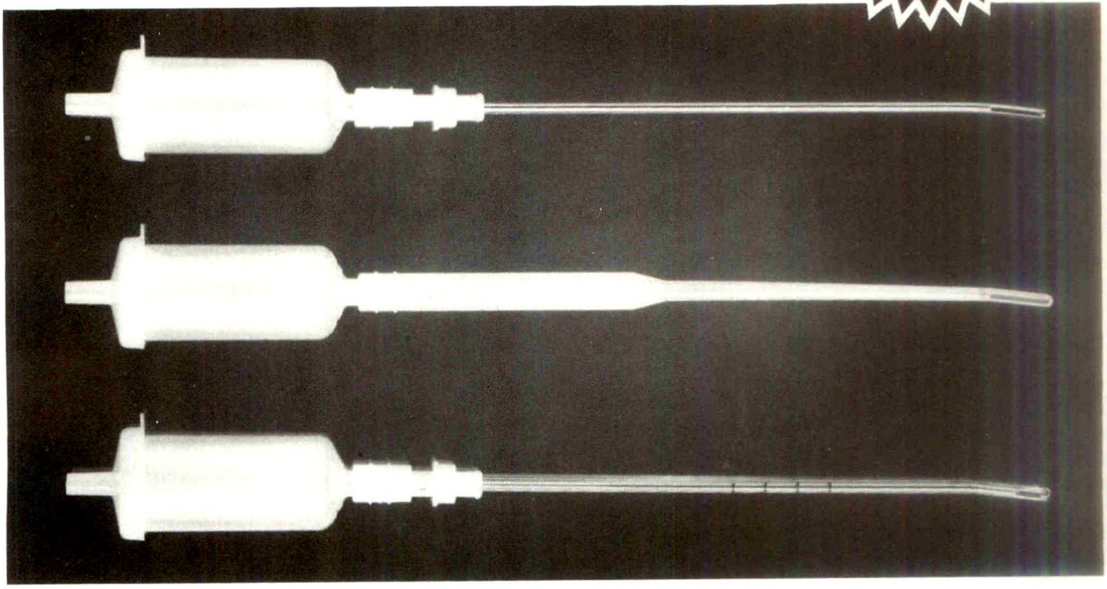

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COMMENTARY

An oxytocin inhibitor for suppressing preterm labour

Dr Åkerlund and his colleagues are to be congratulated on publishing in this issue (pp. 1040–1044) the first report of the use of an inhibitor of oxytocin action for the management of preterm labour. Since this was only a pilot study, too much should not be read into the conclusions; but even so the preliminary findings are of great interest and potential importance.

The preparation used is an analogue of oxytocin which acts as a competitive inhibitor of the action of oxytocin on the uterus. Although ethical consent was obtained, only an open trial design seems to have been permitted and only one infusion of limited duration and dosage was administered to each patient. In 13 patients in uncomplicated preterm labour, treatment was followed in all by a degree of uterine inhibition. In the majority of patients infused at a rate of 25 μg/min and given a total dose of ≥5 mg of the analogue, inhibition of uterine contractions was total. No effects were noted on the pulse rate of the mother or fetus, nor were there any other side-effects.

Since the analogue exerts its effects only by competitive inhibition of oxytocin, the findings support the concept that oxytocin action is involved in the causation of uncomplicated preterm labour. Since the onset of preterm labour is not associated with increased circulating levels of oxytocin, it is likely to result from increased myometrial oxytocin receptors sensitizing the uterus to the oxytocin level already in the circulation (Fuchs *et al.* 1982). It has also been demonstrated (Fuchs & Fuchs 1984) that normal labour at term is associated with increased myometrial oxytocin receptors and Fuchs *et al* (1984) have shown that there is as high a concentration of these receptors in preterm labour as in early term labour.

Increased uterine sensitivity to pre-existing blood levels of oxytocin may be more important as a cause of uncomplicated preterm labour than of normal labour at term, for uterine production of prostaglandins (PG) seems to be greater in the latter than in the former. Plasma levels of the stable PGF metabolite, PGFM, are lower in preterm than in term labours (Sellers *et al.* 1981), while PGE production by amnion cells is lower in tissues obtained after uncomplicated preterm delivery than after term delivery (Lopez-Bernal *et al.* 1987). Preterm labour associated with chorioamnionitis is different since PGE production by amnion cells is enhanced by products of the bacteria commonly associated with uterine infection (Lamont *et al.* 1985) or by inflammatory changes in the amnion (Lopez-Bernal *et al.* 1987). It may prove that in preterm labour associated with chorioamnionitis, treatment with a specific inhibitor of oxytocin alone will not suppress uterine contractions.

As Dr Åkerlund and his colleagues stress, it is difficult to be certain that uncomplicated preterm 'labour' will progress to preterm delivery since spontaneous resolution of uterine activity occurs in at least half the patients (Anderson 1981). To avoid misdiagnosis, therefore, patients in the study were not treated with the analogue for 2–3 h after admission to make certain that uterine contractions were continuing. Changes in the cervix were also detected in all the patients treated, but since the Bishop scores ranged only between 3 and 6, the labour process was not very far advanced. Of the 13 patients, 7 seemed to be treated in Swedish, and 6 in Danish centres. Despite additional treatment with terbutaline for recurring labour in all the Swedish patients begun 1–3 days after the analogue infusion, two patients were delivered preterm, 1 and 2 weeks later. In three of the Danish patients, prophylactic ritodrine was also administered but one of them was delivered preterm.

Of the 13 women treated with the analogue, therefore, 3 (23%) were delivered preterm while in 10 (77%), pregnancy continued to at least 36 completed weeks. Without controls these results cannot be interpreted. If all 13 women, untreated, would have been delivered preterm, treatment was extremely effective. But of women admitted to the John Radcliffe Hospital in 1978 with uncomplicated preterm 'labour' and intact membranes, 83% subsided, largely without treatment, and pregnancy continued to term (Anderson 1981). If this was to have been the outcome in the 13 patients, treatment might have had no effect at all. A large, randomized controlled trial is clearly required and the authors have indicated their awareness of the need.

Even if the analogue proves no more effective than other agents for suppressing uterine contractions (tocolysis), it would have the advantage of freedom from side-effects which are a significant problem with all the many other tocolytic agents including alcohol, prostaglandin synthase inhibitors, calcium antagonists, diazoxide and magnesium sulphate, as well as the beta adrenoceptor agonists which have been the agents most widely used and most extensively investigated. Since they influence cyclic AMP in the cells of all tissues with beta adrenoceptors, they have many effects apart from inhibiting uterine contractions, including maternal tachycardia, tremor, hypokalaemia, diabetogenic effects and others. According to Creasy & Katz (1984) the most serious effects of these drugs are on the cardiovascular system, the most frequent in the USA being hypotension, cardiac arrhythmia, myocardial ischaemia and pulmonary oedema. While hypotension has been a rare complication of beta adrenoceptor agonists introduced since the earlier drugs, the large number of other effects on maternal physiology (Grospietsch & Khun 1984) limits their therapeutic effectiveness.

It can be argued that even the perfect tocolytic would only be of limited value in preterm labour. In more than half the patients, preterm labour is associated with a serious complication such as antepartum haemorrhage and attempting to delay delivery is inadvisable. In the *uncomplicated* preterm labours in which tocolysis might be useful, perinatal mortality is now very low (Chng 1981; review by Turnbull & Lopez-Bernal 1985). In any case, although betamimetic drugs seem effectively to delay delivery for at least 24 h and slightly reduce the proportion of births before 37 weeks, they do not reduce the incidence of low birthweight or perinatal mortality (King *et al.* 1985; Calder & Patel 1985). Such arguments have encouraged some UK obstetric units to use beta adrenoceptors only on very limited indications. In the John Radcliffe Hospital catchment area, this approach has neither increased the incidence of preterm delivery nor adversely affected perinatal mortality, which in 1986 was 4·8/1000 births.

Preterm birth nevertheless remains the single most important cause of neonatal mortality in normally formed babies (Rush *et al.* 1976). Although currently available tocolytics have a potential for reducing neonatal mortality and morbidity, possibilities for improvement certainly remain. There is, therefore, no justification for therapeutic nihilism (King *et al.* 1985). Until the analogue reported by Dr Åkerlund and his colleagues, there has been no effective tocolytic agent without potentially troublesome side-effects. If further work confirms the effectiveness and freedom from side-effects of this new agent it may signal the beginning of a breakthrough in a difficult field. This new analogue deserves to be properly assessed in a randomized controlled trial large enough to ensure that its conclusions are completely convincing.

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Colposcopy: who, when, where and by whom?

Just under 2000 women each year die in England and Wales from cervical cancer (British Medical Association 1986). In recent years there has been no significant fall in these numbers and the proportion of deaths amongst women under 35 years of age in particular has risen sharply. Predictions are for this increase to continue. There has also been an alarming increase in the number of abnormal smears suggesting the precancerous stage, cervical intraepithelial neoplasia (CIN), which some authorities have referred to as an 'epidemic' (Wolfendale *et al.* 1983). It is probable that the increase in available colposcopy services has resulted in a reduction in the number of deaths from cervical cancer.

Despite these increased facilities however, Beral (1986) has predicted that there will be a 60% increase in cervical cancer registrations and a 70% increase in mortality in the under 50 age group over the next 10 years. As cervical screening, colposcopy and appropriate local therapy potentially offer prevention against cervical cancer, it is obviously desirable that there should be an expansion of colposcopy services. The questions that require to be answered, therefore, are who should be colposcoped, when, where and by whom?

Who?

McIndoe *et al.* (1984) reported the results of the follow-up of several hundred patients in New Zealand with CIN 3 (carcinoma *in situ*) who were left untreated with residual disease after the diagnosis had been confirmed by biopsy in the 1950s. After 10 years 18% and after 20 years 36% of these women had developed invasive cancer. It is clear therefore that any patient with a cervical smear suggesting CIN 3 should be referred for colposcopy, biopsy and appropriate local therapy (Singer & Walker 1982). Until recently it had been thought that the milder CIN abnormalities regressed spontaneously in an appreciable number of patients. But these were cytological or histological studies in which much of the lesion had been removed (in some cases the lesion will have been removed in its entirety) and so they were not true natural history studies. In all studies where colposcopy was used in addition to cytology to investigate the natural history of unbiopsied CIN lesions, no major degree of regression has been found (Richart & Barron 1969; Coppleson 1970; Campion *et al.* 1986).

In the most recent study, in London, on the natural history of CIN 1 lesions (Campion *et al.*

1986), of 100 women with cytological and colposcopic evidence of CIN 1, regression occurred over a 2-year period in only seven patients. In 26 women the lesion had progressed to CIN 3 within these 2 years. These data suggest that all women with smears suggesting CIN, no matter how minor the abnormality predicted, should be examined by the illuminated magnification available at colposcopy. A recent editorial has confirmed this view (Fox 1987).

However, with the limited resources at present available, most centres will only be able to offer colposcopy to women with smears suggesting CIN 2–3, women over the age of 35 with smears suggesting CIN 1 and those younger women who have recurrent mildly abnormal cytology reports.

When?

Although it may take several years for a CIN 3 lesion to develop into invasive cancer, it is not known exactly when the progression may occur. Women presenting with metastatic malignant disease in their 20s are becoming increasingly common. It is clear, therefore, that women with a smear suggestive of CIN 3 should be colposcoped as soon as possible after the abnormal finding and certainly within 6 weeks. A recent report from Tayside (Walker *et al.* 1986) has confirmed what many workers in the field had suspected, that cervical smears tend to undercall the severity of CIN in many cases. It is our experience and that of most workers in this field that about one third of patients referred for colposcopy because of recurrent mildly abnormal smears have a CIN 3 lesion on biopsy In the Tayside study 70% of women seen because of smears showing 'mild squamous atypia' had CIN 3 at colposcopy and biopsy. Therefore, although most clinics who endeavour to see patients with smears suggesting CIN 1 give first time appointments at longer intervals than to patients with smears suggesting CIN 3, this may in some cases be an inappropriate, if an unavoidable, system to employ.

Where?

Many clinics are experiencing a doubling of new patient colposcopy appointments every year which places understandable strains not only on medical, nursing and clerical staff and on equipment resources but also, on a simpler level, on the space available. Because of the close association between genital wart virus infection and CIN and invasive cancer (Singer *et al* 1984) many now believe that human papillomavirus (HPV) may be an important part of the aetiological process in cervix cancer One study has shown that over 30% of women with vulval warts have histological evidence of CIN (Walker *et al.* 1983). Many women at risk of cervical cancer attend sexually transmitted disease (STD) clinics either with vulval warts, as the consorts of males with penile warts or with some other sexually transmitted disease. It would seem sensible therefore to consider siting clinics within STD departments Health centres and general practices are other areas which may also one day be considered although at first sight they might seem unlikely (Kitchener *et al* 1987; Chomet 1987).

By whom?

Many physicians in STD clinics have already begun purchasing colposcopes and many have attended the training courses in colposcopy run by the British Society for Colposcopy and Cervical Pathology (BSCCP). An increasing number of general practitioners are also attending these courses. It would be incorrect, therefore, to see colposcopy as the sole preserve of the gynaecologist and indeed the Vice President of the BSCCP is himself a pathologist and not a gynaecologist. Equally, all agree that colposcopy and associated local destructive therapy should only be performed by trained experts. It is desirable that a practising colposcopist should have been supervized in over 100 colposcopies by an acknowledged expert before he practises on his own, and if he is not a gynaecologist himself he must have strong, practical working links with his gynaecological colleagues. Many junior doctors who have undertaken some training in gynaecology are attracted to, and later become established in, STD medicine. If colposcopy is to be used on a large scale within STD departments, these doctors are perhaps those most appropriate to be trained to undertake it. Whether or not treatment should be given within the STD department itself is somewhat controversial. Ideally, codes of practice should be established between STD physicians and gynaecologists in each health district.

What of the role of the general practitioner?

The primary care physician is in an excellent position to identify those most at risk for cervical cancer from knowledge of the woman's medical and social history. Until now this has been used to select those who should be screened by cervical cytology, but increasingly general practitioners are becoming involved in colposcopy. The general practice setting is probably not ideal for colposcopy, except in exceptional circumstances. The role of the general practice clinical assistant or associate specialist within the context of the hospital-based colposcopy service is an entirely different matter. It is hard to envisage how the increasing number of patients to be seen can be managed without the help of a large increase in the number of trained colposcopists. A consultant-based clinic may rely on junior staff to increase the number of patients seen, but each junior staff member must first be trained and after a matter of months, or at the most 2 years, will be moving to another position usually within a different health district. The general practice specialist assistant on the other hand, once trained, can be an invaluable colleague on a much more permanent basis. It is to be hoped that many general practitioners will consider becoming involved in this interesting field in this way.

Finally, any increase in colposcopy services must have revenue consequences in respect of increased funding for associated pathology, cytology, nursing and auxillary services. With the Government's policy of rapid implementation of a call and recall cytology programme already underway, the increasing number of referrals for colposcopy becomes an urgent problem. Indeed with the major funding allocated to the acquired immunodeficiency syndrome (AIDS), the Government must be careful to ensure a reasonable balance between AIDS and cervical cancer funding.

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British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1014–1027

Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy

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Summary. A non-invasive technique for the measurement of cardiac output in pregnancy by combined cross-sectional and Doppler echocardiography at three intracardiac sites is described. The validity of the technique for use during pregnancy is reviewed. Comparison with cardiac output determined simultaneously by the direct Fick technique in 15 non-pregnant subjects showed close agreement for all three measurement sites. Acceptable measurements were obtained from the aortic and pulmonary valves in all pregnant subjects and from the mitral valve in 84% of pregnant subjects. The within-patient intra-observer and hour-to-hour variabilities of cardiac output in pregnant and non-pregnant subjects were <5% of the mean for all three valves studied. Flow measurements at each of the three intracardiac sites correlated closely. The advantages and limitations of the technique for use during pregnancy are discussed.

Lindhard (1915) was the first to measure cardiac output during pregnancy. Since then more than 40 studies have been published on this subject and yet our understanding of maternal cardiovascular physiology is far from complete. Most authorities agree that cardiac output increases by between 30 and 50% during pregnancy (Ueland *et al.* 1969) but the timing of this increase and the pattern of change during the third trimester remain controversial.

Conflicting results may be explained by differences in investigative technique and study design. Early measurements of cardiac output were by the direct Fick and dye dilution methods. These techniques require insertion of catheters into the central circulation and are associated with a small but definite risk (Editorial 1983). Most studies were not longitudinal in design and were of limited value in view of the wide variations between individuals. Lees *et al.* (1967) and Ueland *et al.* (1969) measured cardiac output with dye dilution curves obtained with a continuously recording densitometer. This method avoided the need for multiple arterial samples. Although both were well constructed serial studies, investigations were limited to small numbers of patients at infrequent intervals during pregnancy.

Walters *et al.* (1966), using a photo-electric ear piece, recorded serial dye dilution curves at monthly intervals in 30 pregnant women. They calibrated the ear oximeter by determining the concentration of dye in samples of venous blood withdrawn during the tail of the dye dilution

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curve. Although this method obviated the need for arterial catheterization, the use of venous calibration is associated with large errors (Beard & Wood 1951).

Recently the development of M-mode echocardiography and impedance cardiography has allowed measurements of cardiac output without risk or discomfort to the patient. Furthermore, because subjects are investigated at rest and without sedation, these investigations provide information about haemodynamics in a basal state which may be altered by invasive procedures. A number of longitudinal studies using M-mode echocardiography (Rubler *et al.* 1977; Katz *et al.* 1978; Arima 1982) and impedance cardiography (Atkins *et al.* 1981; Myhrman *et al.* 1982) have been published

Using M-mode echocardiography, stroke volume (SV) can be calculated from the change in the cube of left ventricular internal dimensions. The method has never been validated in pregnancy although correlation with angiographic stroke volume in non-pregnant subjects is relatively high (Pombo *et al.* 1971; Murray *et al.* 1972). The method assumes that the left ventricle is an ellipsoid of revolution, such that the long axis is twice the length of the short axis. This is valid when the ventricular volume is normal but does not hold true when pathological dilatation occurs (Fortuin *et al.* 1971). During pregnancy there is a progressive increase in heart volume (Ihrman 1960) and end-diastolic dimension (short axis) (Katz *et al.* 1978) and the assumptions regarding the shape of the left ventricular chamber may no longer be valid. On theoretical grounds this could lead to an overestimation of stroke volume.

Determination of SV by impedance cardiography depends on the measurement of changes in transthoracic electrical resistance associated with the ejection of blood into the pulmonary circulation (Kubicek *et al.* 1966). Secher *et al.* (1979) compared simultaneous measurements of SV by impedance cardiography and thermodilution during caesarean section. They found a poor correlation between SV determined by the two methods (*r* 0·69, slope 0·84, intercept 10·7). Milsom *et al.* (1983) simultaneously determined SV by impedance cardiography and thermodilution during the third trimester. Although they found a slightly better correlation (*r* 0·87, slope 0·75, intercept 11·2) there was a significant difference between SV values determined by the two methods and the authors concluded that 'the reliability of impedance cardiography for the longitudinal investigation of stroke volume during pregnancy would therefore appear to be limited'. The validity of the assumptions of the Kubicek technique during pregnancy has recently been questioned (de Swiet & Talbert 1986) and results obtained using this method must await confirmation

There is a need for a non-invasive method of measuring cardiac output which is based on assumptions that remain valid throughout pregnancy. Cross-sectional echocardiography combined with Doppler ultrasound measurement of blood velocity provides a method for measuring volumetric flow at specific locations within the heart and great vessels. The principle underlying the method has been validated *in vitro* (Smith 1984; McLennan *et al.* 1986) and in animals (Steingart *et al.* 1980; Fisher *et al.* 1983*a*). Doppler-determined flows across the aortic (Huntsman *et al.* 1983; Loeppky *et al.* 1984, Rose *et al.* 1984), pulmonary (Goldberg *et al.* 1982; Sanders *et al.* 1983) and mitral (Fisher *et al.* 1983*b*; Goldberg *et al.* 1985*a*) valves have been correlated with flows measured by invasive methods. In all cases the correlations have been very high and the absolute measurements have been similar. Therefore calculation of flows from several areas of the heart allows a number of independent estimates of cardiac output. Doppler echocardiography is particularly suitable for the serial measurement of cardiac function and its potential value in the study of haemodynamic changes during both normal and complicated pregnancies is considerable.

The aims of this study were to determine the validity of the Doppler technique compared with the Fick method, to assess the correlation and reproducibility of flow measurements at various intracardiac sites in pregnant and non-pregnant subjects and thus to provide recommendations for the application of the technique in pregnancy.

Theoretical background

The Doppler principle is based on the ability of moving erythrocytes to backscatter ultrasound waves emitted from a transducer at frequencies altered from the emitted frequency. This change in frequency or Doppler shift is proportional to the velocity of the erythrocytes along the axis of the ultrasound beam. The velocity can be calculated from the Doppler equation:

$$V = \frac{\Delta f \times c}{2 f_0 \times \cos \theta}$$

where V = velocity of erythrocytes (cm/s), Δf = measured Doppler frequency shift, c = average speed of propagation of ultrasound in tissue ($\simeq$1540 m/s), f_0 = emitting frequency of the transducer, and θ = angle between the ultrasound beam and the direction of blood flow.

If the Doppler beam is directed parallel to the flow of blood, such that $\cos \theta = 1$, the integral of the velocities over the period of ejection (velocity integral) is equal to the distance that the column of blood moves during each ejection period. Multiplying the velocity integral (VI) by the cross-sectional area (CSA) of the vessel or valve through which the blood flows permits calculation of stroke volume (SV). Further multiplication by the heart rate (HR) gives the flow across the valve.

Both continuous wave and pulsed Doppler can be used to measure velocity. If the ultrasound beam is pulsed, one small area along the beam may be interrogated (range gating). Since the speed of ultrasound through tissue is relatively constant it is possible to determine when information from a given depth will return to the receiving crystal. The area in which range gating is accomplished is conventionally known as the sample volume. Simultaneous display of the sample volume with a cross-sectional image of the heart allows the operator to place the sample volume in a chamber or vessel of interest and to record localized velocities. Simultaneous imaging also allows the beam-flow intercept angle (θ) to be seen in two planes.

With continuous wave Doppler, ultrasound is transmitted continuously and therefore range gating is not possible. Information is received from the entire length of the beam and consequently it is not possible to determine the depth at which the frequency shift has occurred. Continuous wave transducers are not usually combined with imaging transducers with the result that the sampling site cannot be seen. It is not therefore possible to estimate the beam-flow angle.

Subjects and methods

Three separate studies were undertaken. The procedure was explained to each patient and informed consent obtained. Ethical approval was obtained from the ethics committee of Newcastle Health Authority. The patient groups are shown in Table 1.

Validation study

Eighteen adults (12 men and six women, mean age 50, range 13–72 years) admitted for routine diagnostic cardiac catheterization, were recruited. The clinical diagnoses were as follows: aortic coarctation (2), cardiomyopathy (3), mitral valve disease (2), coronary artery disease (11). Three patients, all over 65 years, were subsequently excluded because preliminary echocardiographs were of poor technical quality. In the 15 remaining subjects cross-sectional echocardiographs and Doppler velocities were recorded immediately after completion of the direct Fick procedure and before any contrast studies. No attempt was made to measure mitral flow in the two patients with mitral valve disease. Doppler flows were calculated by one observer who was unaware of the Fick measurements.

All the remaining non-pregnant and pregnant

Table 1. Patient groups

	Number	Age (years) Mean	Age (years) Range	Gestation (weeks)	Number of nulliparae
Validation study	15*	47	13–67	Not pregnant	
Reproducibility study	14	27	23–31	Not pregnant	5
	10‡	28	23–31	16	5
Correlation study	21†	42	13–67	Not pregnant	
	10‡	28	23–31	16	5
	15	26	21–31	38	11

* Three potential subjects were excluded because of poor quality echocardiographs

† Includes the 15 subjects from the validation study.

‡ Same subjects.

subjects were considered to be haemodynamically normal on the basis of physical examinations, ECGs and M-mode echocardiograms.

Reproducibility study

Fourteen healthy non-pregnant women, none of whom was taking a hormonal contraceptive, and 10 healthy women at 16 weeks gestation were recruited (Table 1). In each subject, cross-sectional echocardiographs and Doppler velocities were recorded by the same observer, on two occasions 30–60 min apart. The subjects remained recumbent between each series of recordings. Intra-observer measurement variability was evaluated by re-analysis of the original recordings of heart rate, velocity integral and area in the non-pregnant group. This re-analysis was performed after several weeks so that the observer was unaware of the initial measurements. Temporal variability was assessed by the same observer who analysed echocardiographs obtained 30–60 min apart. The velocity traces were numbered and analysed blindly in random order.

Correlation study

Flow through all three valves was compared in all the patients from the validation study, in the pregnant subjects from the reproducibility study and in an additional six healthy non-pregnant women and 15 women at 38 weeks gestation in a normal pregnancy (Table 1). In each subject, cross-sectional echocardiographs and Doppler velocities were recorded and analysed by the same observer (S.C.R.).

Doppler system

All the echocardiographic recordings were made using a cross-sectional phased-array echocardiographic Doppler system (Hewlett-Packard 77500B). This system utilized a 3·5 MHz phased-array and pulsed Doppler transducer and a 2·5 MHz dedicated independent continuous wave transducer. The equipment performed fast Fourier transform analysis of the Doppler signal and the output was converted to velocity of flow according to the Doppler equation. The Doppler output and an electrocardiographic tracing were recorded on a strip chart at a paper speed of 100 mm/s.

Determination of CO by the direct Fick method

Subjects underwent routine diagnostic right and left heart catheterization. After insertion of the catheters the patients were tilted into the semi-left lateral position. Oxygen consumption was measured using a Waters MRM-2 Oxygen Consumption Monitor. Expired air and room air were mixed and the mixture was analysed for oxygen by a polarographic oxygen sensor. Oxygen consumption, averaged over 20 s, was then displayed digitally. The mean of 10 consecutive readings was used to calculate cardiac output. During the gas collection, blood samples were obtained from the pulmonary artery and the aorta. Pulmonary arterial and aortic oxygen saturations were determined using a reflection oximeter (American Optical Unistat Oximeter) and the results were used to calculate the pulmonary and systemic whole blood oxygen contents. Cardiac output (CO) was calculated using the standard formula:

$$\text{CO (l/min)} = \frac{\text{O}_2 \text{ consumption (ml/min)}}{\text{Arteriovenous O}_2 \text{ difference (ml/l)}}$$

Determination of cardiac output by the Doppler method

In each patient we attempted to measure flow across the pulmonary, mitral and aortic valves. In the group of patients undergoing cardiac catheterization, echocardiographic measurements were performed in the catheterization laboratory after insertion of both catheters. The other patients were studied in a warm quiet room. All the measurements were made in the semi-left lateral position after the subjects had rested for at least 15 min.

Velocity measurements

Pulmonary velocities were recorded from the parasternal short axis plane, using pulsed Doppler ultrasound. The sample volume was placed in the proximal main pulmonary artery (Fig. 1) and the Doppler cursor was aligned parallel with the pulmonary artery walls (Goldberg *et al.* 1982). Mitral velocities were recorded from the apical four-chamber short axis plane using pulsed Doppler. Every effort was made to align the Doppler cursor parallel with the interventricular septum (Fig. 2) and the sample vol-

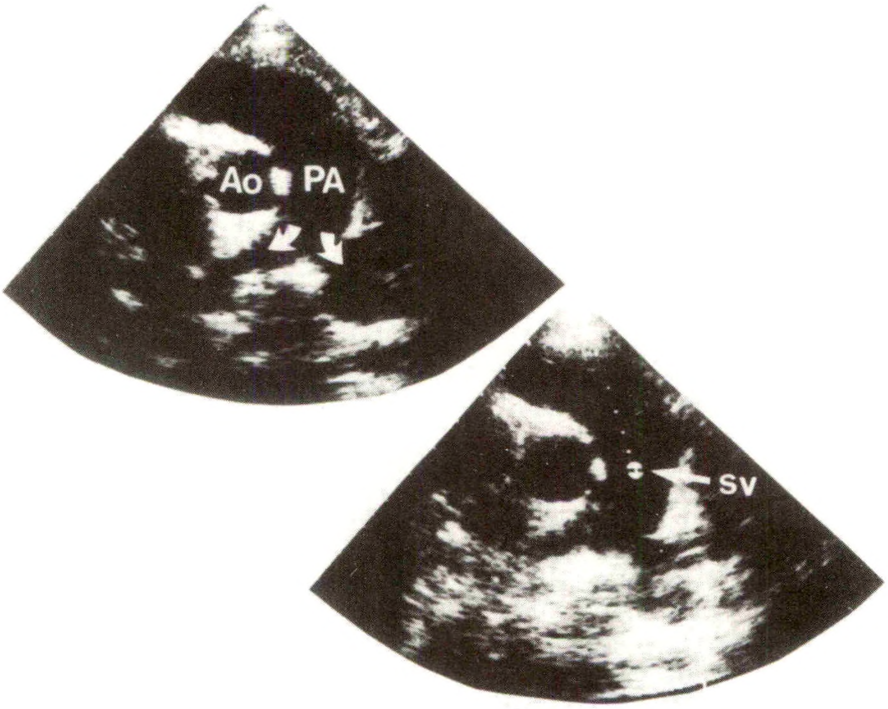

Fig. 1. Cross-sectional echocardiograph. Top: parasternal short axis view at the level of the aorta (Ao) and pulmonary artery (PA). Bottom: same view illustrating the Doppler cursor (dotted line) aligned parallel with the pulmonary artery walls and the sample volume (SV) positioned just distal to the pulmonary valve.

ume was placed just distal to the mitral annulus (Goldberg *et al.* 1985*a*).

For flow calculations θ should ideally be zero or should be accurately determined. In practice this angle cannot be accurately measured from a two-dimensional cross-sectional image. During this investigation we attempted to align the beam parallel to flow in two planes and then tilted the transducer slightly in the third plane until the highest velocities were obtained. At this point we assumed spatial alignment in all three planes.

Ascending aortic velocities were recorded from the suprasternal notch. Initially we tried to measure velocities using the pulsed mode. However, alignment with the ascending aorta was only possible in very few patients due to the size of the transducer. The smaller, off-axis continuous wave Doppler transducer allowed easier interrogation of the ascending aorta and good quality velocity traces were recorded from all patients. The direction of the beam was adjusted until the highest velocities with the least spectral dispersion were found. At this point we assumed that the velocities represented the velocities at the aortic orifice and that the beam was parallel with flow.

The area under the velocity curve (velocity integral) was determined by tracing from the baseline around the velocity curve using a digitizing tablet linked to a microcomputer (Fig. 3) (Goldberg *et al.* 1985*b*). Each determination averaged 8–10 consecutive beats.

Area measurements

Measurements were made from cross-sectional echocardiographs recorded on videotape, using a freeze-frame facility and caliper markers. The pulmonary artery diameter was measured during systole, from the parasternal short axis plane (Goldberg *et al.* 1982). In this plane the artery is imaged in lateral resolution and therefore measurements were made from the centre of the medial wall echoes to the centre of the lateral wall echoes. It was often necessary to rotate the patient to the left in order to image the lateral pulmonary artery wall separate from lung echoes. The aortic diameter was measured in the parasternal long axis plane at the level of the

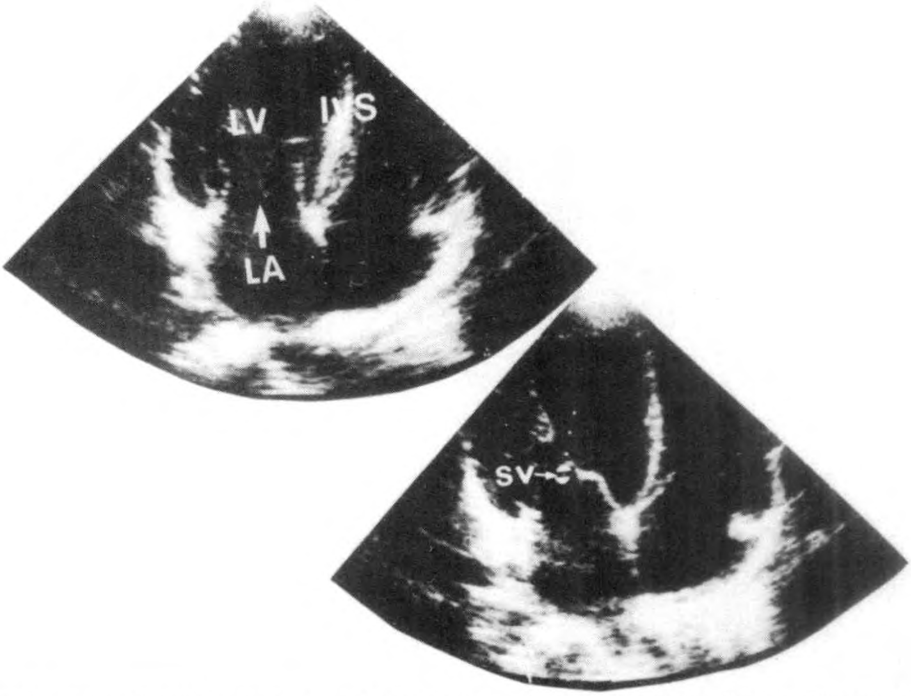

Fig. 2. Cross-sectional echocardiograph. Top: apical four chamber view during diastole, illustrating left atria (LA), left ventricles (LV) and open mitral valve. Bottom: same view during diastole illustrating the Doppler cursor aligned parallel with the interventricular septum (IVS) and the sample volume (SV) positioned between the mitral valve ring and the open valve leaflets.

aortic orifice during systole (Ihlen *et al.* 1984). In this plane the aorta is measured in axial resolution and measurements were made from the leading edge of the anterior wall to the leading edge of the posterior wall. The diameters from five consecutive beats were averaged and the cross-sectional area was calculated from the equation $\pi(D/2)^2$, where D = mean diameter of the aorta or pulmonary artery.

Mitral valve area was measured at the level of the mitral annulus directly from the cross-sectional echocardiograph. In the parasternal short axis plane the mitral valve orifice appeared as a 'fishmouth' which opened during diastole. The maximum annular diastolic orifice was an ellipsoid in shape and could be measured using lateral and axial calipers. These were positioned at the four ends of the axes of the ellipse and the computer within the equipment drew the ellipse and calculated the area. Areas from five consecutive beats were averaged.

Heart rate was determined directly from the R-R interval of the electrocardiogram. Cardiac output was then calculated according to the formula:

$$\text{CO (l/min)} = \text{CSA (cm}^2) \times \text{VI (cm)} \times \text{HR (min}^{-1})$$

where CO = cardiac output, CSA = cross-sectional area, VI = velocity integral, HR = heart rate.

Statistical methods

Cardiac output values were compared by correlation and linear regression analyses. In addition the mean differences and the standard deviations of the differences between measurements of cardiac output by the Fick method and the three Doppler methods were determined (Bland & Altman 1986). A components-of-variance analysis was performed to determine (a) reliability of the measurements made by a single observer (intra-observer variability) and (b) the reproducibility of results from one occasion to the next (temporal variability). Using these estimated variances, the within-patient coefficients

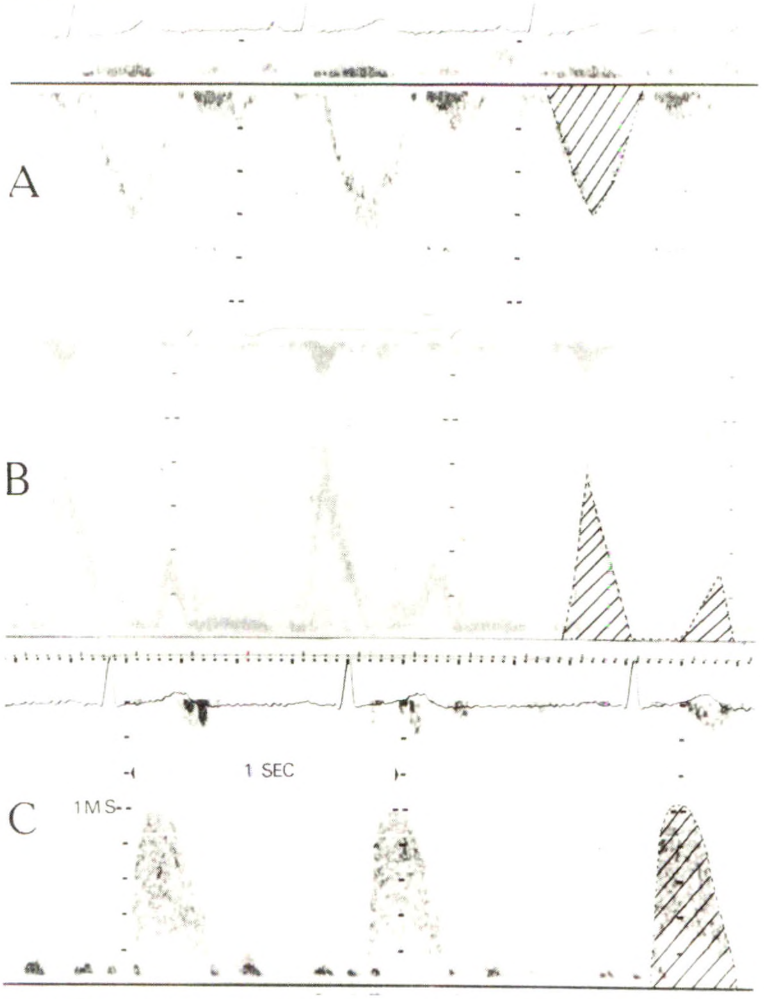

Fig. 3. Typical Doppler velocity traces from (A) pulmonary artery and (B) mitral valve using Doppler and from (C) ascending aorta using continuous wave Doppler. Cross-hatched area indicates the velocity integral (area under the velocity curve).

of variation were determined for heart rate and velocity integral, area and cardiac output at each of the three intracardiac sites.

Results

Doppler cardiac output measurements were obtained on 84 occasions: 15 during the validation study, 48 during the reproducibility study and a further 21 during the correlation study. Each investigation took approximately 30 min to complete. In non-pregnant subjects under the age of 45 years, satisfactory measurements were obtained from all three sites. In those over 45 years, adequate pulmonary measurements could not be obtained in five subjects and adequate mitral measurements in three subjects. Satisfactory aortic and pulmonary measurements were obtained in all pregnant subjects but satisfactory mitral measurements were possible in only 11 out of 15 subjects at 38 weeks gestation.

The correlations between Fick cardiac output and aortic, pulmonary and mitral flows determined by Doppler are shown in Table 2. There was a high correlation at all three sites. None of the slopes was significantly different from unity and none of the intercepts was significantly different from zero. The large standard errors for the intercept are due to the lack of data points at low cardiac outputs. The mean calculated differences between measurements of cardiac output (CO) by the Fick method and the three Doppler

Table 2. Validation study: linear regression analysis

y	on	*x*	*n*	*r*	SD (ml/min)	Slope (SE)	Intercept (SE)
Fick CO		Aortic CO	15	0·93	402	1·00 (0·11)	0·8 (574·6)
Fick CO		Pulmonary CO	13	0·87	556	1·03 (0·17)	−163·2 (891·2)
Fick CO		Mitral CO	13	0·89	512	1·12 (0·16)	−165·7 (803·8)

n, Number; *r* correlation coefficient; SD, residual standard deviation, SE, standard error; CO, cardiac output.

methods were: Fick CO and aortic CO, −10 (SD 340) ml/min; Fick CO and mitral CO, −36 (SD 430) ml/min; Fick CO and pulmonary CO, +227 (SD 404) ml/min. Thus measurements at the aortic valve appear to give the closest agreement with cardiac output determined by the Fick method.

Table 3 summarizes the reproducibility of heart rate, area, velocity integral and cardiac output measurements. Within-patient comparisons are of more relevance in longitudinal studies than between-patient comparisons. Intra-observer variability was much smaller for heart rate (1·4%) than for area (3·0–3·8%), velocity integral (3·4–4·2%) and cardiac output (3·1–3·7%) measurements. Aortic measurements had the lowest coefficients of variation. However, differences between the measurements at any of the three sites were small. Within-patient temporal variability was larger than intra-observer variability. Heart rate showed a small coefficient of variation (2·9%), confirming the haemodynamic stability of the subjects during the investigations. The variability of aortic measurements was consistently less than that found with pulmonary and mitral measurements but again the differences were small. The temporal variability was similar in the pregnant and non-pregnant groups The variability between subjects (not shown) was consistently larger than that within patients.

Figure 4 demonstrates the close correlations between aortic, pulmonary and mitral Doppler flows. The residual standard deviations or standard errors of the estimate (SEE) ranged from 336–467 ml/min and in no relation did the slope differ significantly from zero. The intercept for the mitral-pulmonary relation was significantly greater than zero ($P < 0·05$), suggesting a small but systematic underestimation of pulmonary flow with respect to mitral flow.

The linear regression analyses for flows measured at the three sites in the pregnant and non-pregnant groups are shown in Table 4. The correlation coefficients of aortic and mitral and of aortic and pulmonary flows were very similar in the two groups. There was a lower, although still highly significant ($P < 0·001$), mitral-pulmonary correlation during pregnancy ($r = 0·84$) compared with the non-pregnant group ($r = 0·93$). The residual standard deviations were all small (276–485 ml), confirming the small variability of flow measurements at each of the intracardiac sites. The slope values were consistently lower in the pregnant than in the non-pregnant groups but none of the differences was statistically significant and in no case did the slope differ significantly from unity. The *y* axis intercepts were consistently larger in the pregnant group, especially for the aortic-pulmonary and mitral-pulmonary relations. Again none of the differences was statistically significant and in no case was the intercept significantly different from zero. However, the large standard errors of

Table 3. Reproducibility study: within-patient coefficients of variation in pregnant and non-pregnant subjects

	Intra-observer (%)	Temporal (%)	
		Non-pregnant	Pregnant
Number of paired comparisons	14	14	10
Heart rate	1·4	2·9	2·3
Aortic area	3·0	3·4	3·2
Pulmonary area	3·0	3·7	4·3
Mitral area	3·8	4·0	3·9
Aortic velocity integral	3·4	3·5	2·8
Pulmonary velocity integral	4·2	4·3	4·2
Mitral velocity integral	4·2	4·9	3·6
Aortic cardiac output	3·1	3·6	4·1
Pulmonary cardiac output	3·7	4·8	4·9
Mitral cardiac output	3·4	4·1	3·8

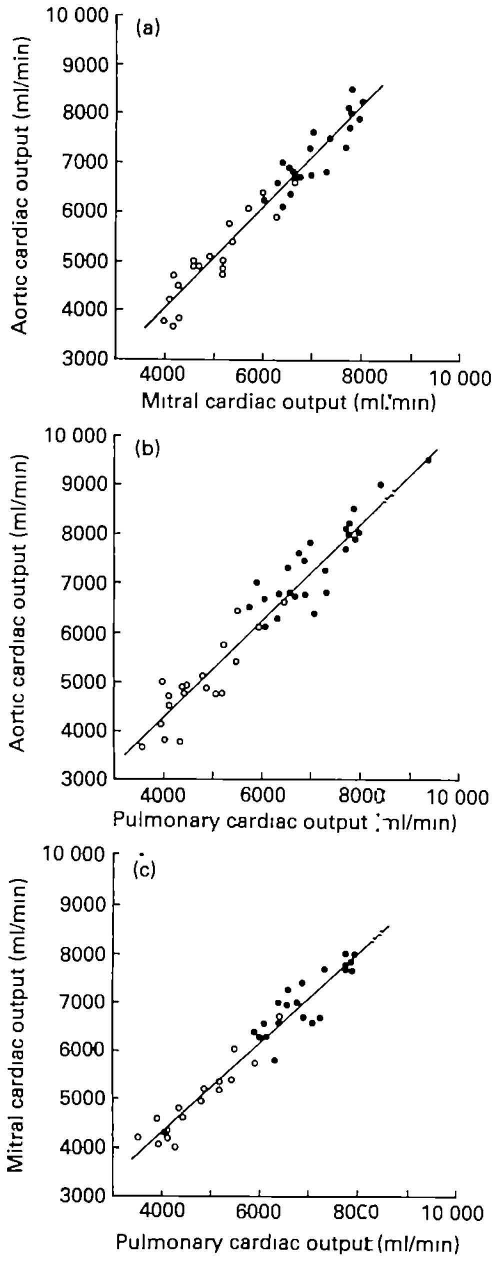

Fig. 4. Regression plots comparing Doppler cardiac output measurements at the (a) aortic and mitral valves; (b) aortic and pulmonary valves; and (c) mitral and pulmonary valves. ●, pregnant; ○, non-pregnant. (a). correlation coefficient (r) = 0·96; n = 40, residual standard deviation (SD) = 370 ml/min; slope (SE) = 1·02 (0·04); y intercept (SE) = −96 (293) (b): r = 0·96; n = 44; SD = 467 ml/min; slope (SE) = 0·97 (0·05); y intercept (SE) = 402 (305). (c): r = 0·97, n = 38; SD = 336 ml/min; slope (SE) = 0·92 (0·04); y intercept (SE) = 618 (251).

the intercept, caused by the lack of data points at low cardiac outputs in the pregnant group, markedly reduced the significance.

Discussion

The combination of echocardiography and Doppler ultrasound provides a unique non-invasive method of measuring cardiac output in pregnancy. It is simple, quick and reproducible and causes no discomfort to the patient.

Calculation of cardiac output by this technique is based upon a number of assumptions which may give rise to error.

Measurement of cross-sectional area (CSA)

Calculation of aortic and pulmonary arterial areas depends on the accurate measurement of vessel diameters. It is assumed that the area through which blood flows is circular and of constant size throughout the period of flow. The assumption of circular geometry is reasonable but the CSA does change during ejection. The variation of CSA during systole is smaller for the proximal aorta (11%) (Greenfield & Patel 1962) than for the pulmonary artery (23%) (Greenfield & Griggs 1963) and this may partly explain the poorer correlation of pulmonary flow with invasively determined flow. Such large changes in CSA are unlikely to occur at the level of the fibromuscular valve orifice and Ihlen *et al.* (1984) reported no change in aortic orifice CSA during systole. Mitral CSA is measured directly from the short axis view and the accuracy is limited by rotational errors in plane alignment and the potential for the heart to shift relative to the short axis plane of view during diastole. This may account for the poorer reproducibility of mitral area compared with aortic and pulmonary areas despite the fact that the percentage error in aortic or pulmonary artery diameter measurement is doubled when the diameter is squared to derive CSA (Ascah *et al.* 1985). The method of determining mitral area also assumes the orifice to be constant geometric shape (ellipsoid) and size. Both the inlet (at the valve annulus) and the outlet (at the free cusp margin) have been shown to be elliptical in shape (Taylor & Whamond 1976; Ormiston *et al.* 1981), however, there are marked changes in the orifice area during diastole. This change is much larger at the valve tips than at the valve annulus and Ormiston *et al.*

Table 4. Correlation study: linear regression analysis

y	on	*x*	Group	*n*	SD (ml/min)	Slope (SE)	Intercept (SE)
Aortic CO		Mitral CO	All	40	370	1·02 (0·04)	−86 (293)
Aortic CO		Mitral CO	P	21	381	0·92 (0·13)	677 (905)
Aortic CO		Mitral CO	NP	19	365	0·98 (0·11)	101 (549)
Aortic CO		Pulmonary CO	All	44	467	0·98 (0·04)	402 (305)
Aortic CO		Pulmonary CO	P	25	485	0·86 (0·11)	1286 (824)
Aortic CO		Pulmonary CO	NP	19	445	0·93 (0·13)	577 (653)
Mitral CO		Pulmonary CO	All	38	336	0·92 (0·04)	618 (251)
Mitral CO		Pulmonary CO	P	21	371	0·78 (0·12)	1668 (834)
Mitral CO		Pulmonary CO	NP	17	276	0·89 (0·09)	735 (410)

n, Number; SD, residual standard deviation; SE, standard error; All, pregnant and non-pregnant groups combined; P, pregnant; NP, non-pregnant

(1981) found only a small increase (≃10%) in annular area during diastole.

Measurement of velocity

Calculation of flow using continuous wave Doppler (where flow is sampled along the entire length of the ultrasound beam) assumes that the maximum velocity recorded corresponds to the velocity at the level where CSA has been measured. With pulsed Doppler, where the sample volume can be placed at a specific depth, velocity and CSA can be sampled at the same level. It must also be assumed that the velocity recorded represents the velocity across the entire cross-sectional area of the vessel or valve. This assumption is true if the velocity profile is flat. The velocity profile is dependent on flow acceleration, geometric factors and viscosity (Skjaerpe *et al* 1985). Acceleration and convergence of flow, as occurs in the ventricular outflow tracts and in the immediate proximity of the semilunar valves, flattens the velocity profile and there is some evidence in man to suggest that a flat velocity profile at these sites is a reasonable assumption (Schultz *et al.* 1969; Seed & Wood 1971; Taylor & Whamond 1976). The effect of viscosity on velocity measurements is complex and poorly understood. Daniel *et al.* (1986) reported a weak but significant negative correlation between aortic velocity integral and haemoglobin concentration ($r = -0{\cdot}38$, $P < 0{\cdot}05$). Their data would suggest that for a change in haemoglobin concentration of 1 g/dl, the aortic velocity integral will change by 0·5–0·6 cm. During human pregnancy the haemoglobin concentration may fall by 2 g/dl (Hytten & Lind 1973). The related decline in blood viscosity will lead to an overestimation of Doppler-determined velocity but failure to correct for these viscosity changes would lead to an overestimation of cardiac output of only 5%.

Calculation of velocity ideally requires knowledge of the beam-flow intercept angle. In practice this angle cannot be measured accurately from a two-dimensional image because of the problem of estimating the angle in the third (elevational) plane. During these investigations it was assumed that the Doppler beam was parallel to flow and therefore that cos θ was equal to 1. Provided that the intercept angle was within 20° of the flow axis the velocity would have been underestimated by less than 6%.

Despite these theoretical problems we have found close correlations between Fick CO and Doppler cardiac output calculated from the aortic, pulmonary and mitral valves in non-pregnant subjects. Our results confirm previous reports that CO measured at the aortic valve compares better with invasive CO measurements than flows measured at the mitral valve (Lewis *et al.* 1984; Goldberg *et al.* 1985*a*; Gillam *et al.* 1985) and pulmonary valve (Goldberg *et al.* 1982; Labovitz *et al.* 1985). Because of the size of the transducer we were unable to obtain acceptable aortic velocities using the pulsed mode. In this we differed from these other workers. However, our correlation for aortic Doppler and Fick cardiac output is similar to that obtained using the pulsed mode.

Although there appears to be no systematic difference between results obtained using the Fick and Doppler methods there were significant differences between the calculated cardiac output in a number of paired measurements. Even larger individual differences have been reported when the Fick method has been compared with the dye dilution method. Taylor & Shillingford (1959) made 53 comparisons and found that 23% of measurements gave a >25% difference between the two methods. A major problem in assessing studies that compare various cardiac output measurement techniques, including Doppler, is not knowing which measurement is the most accurate. We can only measure how reproducible a technique is and how well it compares with other methods.

We obtained satisfactory measurements of velocity and area from the aortic and pulmonary valves in all of our pregnant subjects. Adequate display of the proximal pulmonary artery is easier in thin young subjects (Goldberg *et al.* 1985*b*) and it seems probable that the discrepancies which we found between pregnant and non-pregnant groups were related to differences in age and physique. It is noteworthy that satisfactory pulmonary measurements were obtained from all non-pregnant subjects in the reproductive age group. We were unable to record acceptable mitral velocities in 27% of pregnant subjects at 38 weeks gestation. This difficulty would appear to be peculiar to pregnancy as good quality mitral measurements are obtainable in between 90 and 100% of non-pregnant subjects (Lewis *et al.* 1984; Goldberg *et al.* 1985*a*). In each of our unsuccessful cases there was marked cephalic displacement of the apex, and poor quality apical images made alignment of the sample volume with the interventricular septum impossible.

A major advantage of ultrasound to measure cardiac output is the ability to use the technique serially in the same individuals. The variability which may occur with time and due to observer technique must be known in order to interpret accurately changes in serial measurements. The within-patient intra-observer and hour-to-hour variabilities were all small (<5% of the mean), and hour-to-hour variability was unchanged during pregnancy. In the present study aortic measurements were least variable in both the pregnant and non-pregnant groups. Gardin *et al.* (1984) reported the intra-observer and day-to-day variability of aortic velocity integral measurements, expressed as the percentage difference between measurements, to be 3·2% and 3·8% respectively. McLennan *et al.* (1986) also quoted percentage differences between measurements and reported the reproducibility of paired measurements of minute distance (velocity integral × heart rate) to be 5·4%. To date there have been no reports concerning the reproducibility of pulmonary and mitral measurements.

We measured flow at three sites within the heart allowing three independent measurements of cardiac output. For the whole study population the correlation of flows measured at the three sites was excellent although there was a tendency to underestimate pulmonary flow relative to mitral flow. There is no obvious explanation for this finding. Loeber *et al.* (1984), using pulsed Doppler to compare the flows distal to the four cardiac valves, reported a similar correlation between aortic and pulmonary flow. Much poorer correlations, however, were found between pulmonary and mitral flow (*r* 0·59, SEE 1586 ml/min, slope 0·70, intercept 1028 ml/min) and aortic and mitral flow (*r* 0·59, SEE 1591 ml/min, slope 0·73, intercept 953 ml/min). In that study mitral orifice area was calculated using the method described by Fisher *et al.* (1983*b*) which systematically underestimated mitral flow. Goldberg *et al.* (1985*a*) measured mitral flow using a simpler elliptical area method similar to that used in the present study. They reported an improved correlation with aortic flow (*r* 0·96, SEE 516 ml/min, slope 0·90, intercept 297 ml/min) and a close correlation with invasively determined flow (*r* 0·93, SEE 435 ml/min, slope 0·81, intercept 825 ml/min). In the present study the correlation coefficients were generally slightly lower in the pregnant group than in the non-pregnant group, although they all remained highly significant ($P < 0{\cdot}001$).

There have been few reports describing the use of Doppler ultrasound for the measurement of central maternal blood flow. Newman (1982) first used the technique in pregnancy to measure changes in mean aortic velocity during caesarean section. James *et al.* (1984) measured cardiac output using continuous wave Doppler and A-mode echocardiography during caesarean section and subsequently reported the first serial study of cardiac output using this technique during pregnancy (James *et al.* 1985). They studied seven subjects during pregnancy and again >4 weeks after delivery. Unfortunately only percentage changes in cardiac output were reported. Cardiac output decreased significantly between the end of the second trimester and the puerperium but no other significant change was identified.

Haites *et al.* (1985) also studied aortic velocity in pregnancy. They developed the concept of linear cardiac output or minute distance, derived by multiplying the aortic systolic velocity integral by the heart rate. This has the potential advantage that the inaccuracies and assumptions of cross-sectional area (CSA) measurement are avoided. They used continuous wave Doppler ultrasound to measure the velocity in the aortic arch and reported a 56% increase in minute distance compared with non-pregnant values at a mean gestation of 19 weeks. The same group has recently reported a longitudinal study of velocity integral and minute distance during pregnancy (McLennan *et al.* 1987). They found a maximum increase in minute distance of 37% in the supine and 30% in the left lateral position at 16 and 24 weeks respectively. If the aortic CSA remained constant during pregnancy then these increases in minute distance would accurately reflect a rise in cardiac output. However, there is evidence that the aortic CSA increases by 14–23% in pregnancy (Katz *et al.* 1978; Hart *et al.* 1986). Animal studies further suggest that increasing flow through the aortic valve results in not only a velocity increase but also a rise in CSA (Stewart *et al.* 1985). Measurement of minute distance may therefore tend to underestimate cardiac output because it fails to take into account the increase in aortic CSA. To date there has not been a satisfactory longitudinal study of volumetric cardiac output using Doppler ultrasound for comparison.

We conclude that combined Doppler and cross-sectional echocardiography is a widely applicable, non-invasive technique that allows accurate and reproducible measurement of cardiac output at a number of cardiac sites during pregnancy. Aortic measurements provide the most reproducible and accurate estimation of cardiac output and these can be obtained simply and quickly in most if not all pregnant subjects. Providing the technique is applied systematically and the sources of error are understood there seems little doubt that it will become increasingly useful in clinical obstetric practice, not only in the investigation of normal cardiovascular adaptations but also in the assessment of haemodynamic changes in patients with cardiac disease and severe hypertension.

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Received 27 October 1986
Accepted 25 June 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1028–1039

Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study

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Summary. Serial haemodynamic investigations were performed in 15 women at 38 weeks gestation and then 2, 6, 12 and 24 weeks after delivery. Cardiac output was measured by Doppler and cross-sectional echocardiography at the aortic, pulmonary and mitral valves. Cardiac chamber size and ventricular function were investigated by M-mode echocardiography. Flow measurements at the three intracardiac sites correlated closely. Cardiac output fell from a mean of 7·42 l/min at 38 weeks to 4·96 l/min at 24 weeks after delivery, a fall of 33%. Most of this decrease (28%) had occurred by 2 weeks. This was associated with a 20% reduction in heart rate and an 18% reduction in stroke volume. By 2 weeks after delivery there was a significant decrease in left atrial dimension and left ventricular end-diastolic dimension. Left ventricular wall thickness and mass declined throughout the period of study as did aortic, pulmonary and mitral valve areas. M-mode derived indices of myocardial contractility were all significantly reduced by 2 weeks and thereafter showed no further change. No haemodynamic differences were found between lactating and non-lactating mothers.

Pregnancy is a time of dramatic haemodynamic readjustment, characterized by an increase in cardiac output of between 30 and 50%. Cardiac output varies widely between individuals, and it is best to study cardiodynamic changes serially in the same patients, but because early investigators relied on invasive techniques, there were few serial studies (Walters *et al.* 1966; Lees *et al.* 1967; Ueland *et al.* 1969). With recent non-invasive techniques such as impedance cardiography and echocardiography sequential studies in individual patients have become possible (Katz *et al.* 1978; Atkins *et al.* 1981; Myhrman *et al.* 1982). Unfortunately these techniques involve assumptions that may not be valid during pregnancy (de Swiet & Talbert 1986; Robson *et al.* 1987). All investigators have concentrated on circulatory changes during pregnancy and few have performed repeated measurements in the puerperium so that the circulatory readjustments after delivery have not been adequately documented.

Cardiac output can be measured by cross-sectional echocardiography combined with Doppler ultrasound, a technique which permits measurement of blood velocity at a point in the circulation where the cross-sectional area (CSA) can also be measured (Goldberg *et al.* 1985). The technique is reproducible (Gardin *et al.* 1984; Robson *et al.* 1987) and allows easily repeatable, non-invasive measurements of cardiac blood flow without discomfort to the patient.

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M-mode echocardiography is a non-invasive technique that allows accurate and reproducible measurements of cardiac chamber size and ventricular performance (Murray *et al.* 1972; De Maria *et al.* 1979). We have used this technique in combination with cross-sectional and Doppler echocardiography to measure serially the haemodynamic changes that occur after childbirth.

Patients and methods

Fifteen healthy women with uncomplicated singleton pregnancies were recruited at 38 weeks gestation from the antenatal clinic. Their clinical details are shown in Table 1. Fifteen non-pregnant women of similar age (six nulliparous, nine multiparous), none of whom was taking a hormonal contraceptive, were recruited as controls. No patient had any evidence of cardiovascular disease. The procedure was carefully explained to each patient and informed consent was obtained. The experimental protocol was approved by the ethics committee of Newcastle Health Authority. Subjects were studied at 38 weeks gestation and then 2, 6, 12 and 24 weeks after delivery. Control subjects were studied once during the luteal phase of a normal menstrual cycle.

On each occasion the patients were asked to attend having fasted and refrained from smoking for 2 h. They rested on a couch in the semi-left lateral position in a warm, quiet room. Measurements of heart rate (HR) and blood pressure (BP) were made every 5 min and the echocardiographic investigations were started when the patient was considered haemodynamically stable (three consecutive readings of HR and BP within 5%). Blood pressure was measured with a cuff sphygmomanometer and diastolic BP was taken as the muffling of the Korotkoff sounds (phase 4). The last recorded BP was used for analysis. After the echocardiographic investigations a sample of blood was obtained for estimation of haemoglobin and haematocrit.

Table 1. Patient details

No of patients	14
Age (years)	26·3 (3 4)
Primigravidae (*n*)	11
Mode of delivery	
Normal (*n*)	10
EBL (ml)	210 (75)
Forceps (*n*)	3
EBL (ml)	366 (57)
Caesarean section (*n*)	2
EBL (ml)	500 (70)
Birthweight (kg)	3·48 (0·33)
Mode of feeding	
Breast	11*
Bottle	4
Contraception	
Combined pill	3
Progestogen-only pill	7
Intrauterine device	3
None	2

Results are mean (SD) values.
* Seven were still breast feeding at 24 weeks.
EBL, Estimated blood loss.

All the investigations were performed using a cross-sectional phased-array echocardiographic Doppler system (Hewlett-Packard 77500B). Velocity and area measurements were performed at the pulmonary, mitral and aortic valves, allowing three independent estimates of cardiac output. The principles and techniques used have been described previously (Robson *et al.* 1987).

Standard left ventricular M-mode echocardiographs (Fig. 1a) were obtained from the parasternal long axis view by placing the transducer in the third or fourth intercostal space at the left parasternal border. The M-mode cursor was then positioned immediately below the plane of the free edges of the mitral valve, perpendicular to the left ventricular cavity (Roelandt 1983). Using the same view, standard left atrial echoes (Fig. 1b) were obtained by positioning the cursor in the plane of the aortic valve perpendicular to the left atrium (Roelandt 1983). M-mode echocardiographs were recorded on a strip chart with an electrocardiogram at a paper speed of 100 mm/s.

Left ventricular dimensions were measured from the endocardial surfaces of the posterior wall and the left side of the septum. The end-diastolic dimension (EDD) was measured at the peak of the R wave on the electrocardiogram and the end-systolic dimension (ESD) at the point of closest approximation of the posterior wall and the interventricular septum (Kaye *et al.* 1975). The posterior left ventricular wall thickness (PWT) and the interventricular septal thickness (IVST) were measured at the peak of the R wave and summated to give the total left ventricular wall thickness. Left atrial dimension was measured at the widest point during atrial

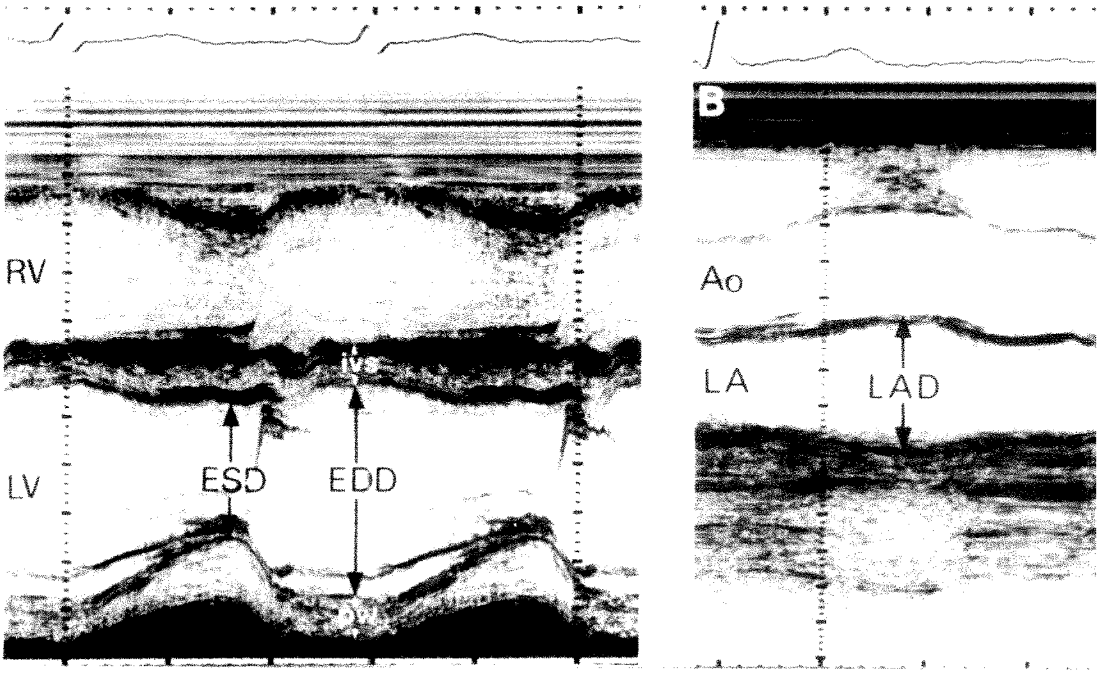

Fig. 1. M-mode echocardiographs of (A) left ventricle and (B) left atrium. RV, Right ventricle; LV, left ventricle; ESD, end-systolic dimension; EDD, end-diastolic dimension; ivs, interventricular septal thickness; pw, posterior wall thickness; Ao, aorta; LA, left atrium; LAD, left atrial dimension.

diastole (Brown *et al.* 1974). Four consecutive beats were averaged for each dimension.

A number of indices of left ventricular function were recorded. The peak systolic and diastolic rates of change of dimension of the left ventricular cavity (LV dD/dt) were determined by digitizing the outlines of the left ventricular cavity throughout one cardiac cycle. This technique has been described previously (Griffiths *et al.* 1982). The peak systolic rates of change of dimension are a measure of left ventricular contractility. Three consecutive beats were averaged for each determination. Ejection fraction (EF) was calculated using the mean left ventricular measurements from the following formula (Feigenbaum *et al.* 1969):

$$\text{EF}\ (\%) = \frac{(\text{EDD})^3-(\text{ESD})^3}{(\text{EDD})^3}$$

The mean velocity of circumferential fibre shortening (mean Vcf) was calculated using the mean left ventricular measurements from the following formula (Karliner *et al.* 1971):

$$\text{Mean Vcf (Diam/s)} = \frac{\text{EDD}-\text{ESD}}{\text{Ejection time}\times\text{EDD}}$$

Left ventricular ejection time was obtained from the aortic velocity trace. Left ventricular mass (LV mass) was calculated using the mean left ventricular measurements from the following formula (Devereux & Reichek 1977):

$$\text{LV mass (g)} = 1{\cdot}04\ (\text{EDD}+\text{PWT}+\text{IVST})^3-(\text{EDD})^3-13{\cdot}6$$

All measurements were made by one observer (S.C.R.). To eliminate bias, vessel and valve areas were determined blindly without knowledge of previous results or velocity measurements.

Statistical methods

A repeated measures analysis of variance was performed for each variable using the statistical package BMDP. This method of analysis adjusts for correlated observations in individual patients. If the overall analysis of variance suggested a difference in the means of a variable, multiple paired comparisons were used to determine at which time points the means differed significantly. The statistical significance of the various mean values for the lactating and non-lactating groups was tested by Student's t-test. The significance of the differences between the study group at 24 weeks after delivery and the control group was also tested by Student's t-test.

Results

Each investigation took on average 30 min to complete. Good quality aortic and pulmonary velocity traces were obtained in all patients. Satisfactory mitral velocities proved more difficult and good quality traces were obtained in only 11 patients. Measurements of cardiac output from the aortic, pulmonary and mitral sites correlated closely (r 0·91–0·92, residual standard deviation 419–502 ml/min). There were no significant differences in any of the variables, at any of the time points studied, between the normal and 'abnormal' delivery groups. The results for the whole group are therefore presented together.

The cross-sectional and Doppler echocardiographic results are shown in Table 2. There was a 21% decrease in HR by 2 weeks after delivery and thereafter no further significant change was demonstrated. Left ventricular ejection time showed a reciprocal increase.

Aortic, pulmonary artery, and mitral valve areas all declined throughout the postnatal period, representing decreases, relative to the end of pregnancy, of 8%, 11% and 12% respectively. The corresponding velocity integrals were significantly decreased by the second postnatal week. Thereafter there was an insignificant but consistent increase between 2 and 6 weeks followed by a further decrease. The lowest values were found at 24 weeks after delivery and represented decreases of 8%, 13% and 9% for the aortic, pulmonary, and mitral velocity integrals respectively. Stroke volumes, calculated using the Doppler method, fell progressively throughout the postnatal period and the pattern of change was consistent for the three sites of measurement. By the second week decreases of between 8 and 10% had occurred; by 24 weeks further significant decreases had occurred to values 17 to 19% below those obtained in late pregnancy.

The changes in cardiac output (Fig. 2) were similarly consistent for the three sites. There were highly significant decreases of between 27 and 29% by 2 weeks after delivery. Thereafter

Table 2. Cross-sectional and Doppler echocardiographic results

	Pregnancy 38 weeks	Postnatal (weeks) 2	6	12	24	SEM
Heart rate (beats/min)	87	69***	67***	67***	69***	2
Left ventricular ejection time (ms)	270	286***	296***	301***	296***	3
Aortic area (cm^2)	4·44	4·33**	4·22**	4·05***	3·97***	0·05
Pulmonary artery area (cm^2)	7·16	7·19	6·96	6·68***	6·61***	0·08
Mitral valve area (cm^2)	7·58	7·26**	7·22**	6·89***	6·69***	0·08
Velocity integral (cm)						
Aortic	20·0	18·7*	19·0	19·4	18·4*	0·4
Pulmonary	12·2	11·2**	11·6	11·1**	10·6***	0·2
Mitral	11·7	11·0**	11·2	11·0**	10·8**	0·2
Stroke volume (ml)						
Aortic	88·3	80·7**	80·3**	78·4***	73·4***	1·7
Pulmonary	87·1	80·0**	81·4*	74·1***	70·3***	1·8
Mitral	88·5	79·9**	80·1**	76·6***	72·5***	1·9
Cardiac output (l/min)						
Aortic	7·60	5·56***	5·35***	5·21***	5·02***	0·13
Pulmonary	7·44	5·43***	5·36***	5·00***	4·93***	0·15
Mitral	7·21	5·13***	5·27***	5·03***	4·93***	0·14

Values quoted are means. The standard error of the mean (SEM) was determined from the analysis of variance and was based on the intra-patient variability.

P (probability) values indicate significant differences from values at the end of pregnancy; *$P<0{\cdot}05$, **$P<0{\cdot}01$, ***$P<0{\cdot}001$

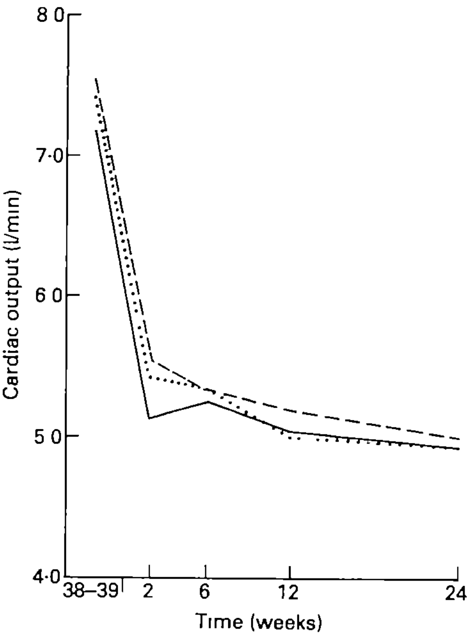

Fig. 2. Serial measurements of maternal cardiac output, measured at the mitral (———), pulmonary (. .) and aortic (– – –) valves, at 38 weeks gestation and throughout the puerperium.

there was a more gradual decline to minimum values at 24 weeks of between 32 and 34%. The decrease between 2 and 24 weeks was significant for the pulmonary ($P<0·01$) and aortic ($P<0·01$) flows only.

M-mode measurements are shown in Table 3. Left ventricular end-systolic dimension showed no significant change after delivery. End-diastolic dimension was significantly reduced by 2 weeks after delivery. Although there was a further progressive decline until 24 weeks, the difference between 2 and 24 weeks was not significant. Left atrial dimension showed a similar pattern of decline, reaching significance at 2 weeks and thereafter showing no further decrease. These changes represent a reduction in end-diastolic and left atrial dimensions, relative to the end of pregnancy, of 4% and 11% respectively.

Total left ventricular wall thickness decreased throughout the postnatal period. This decrease was significant by 12 weeks. The difference between 12 and 24 weeks was significant ($P<0·05$). As expected left ventricular mass also decreased, since this measurement is derived from left ventricular wall thickness. The decrease in mass between 6 and 12 weeks was significant ($P<0·01$).

The peak rate of change of dimension in systole, the ejection fraction and the mean rate of circumferential fibre shortening were all significantly reduced by 2 weeks after delivery. There were no further significant changes in any of these indices of contractility after this time. The peak rate of change of dimension in diastole, which may be a measure of ventricular com-

Table 3. M-mode results

	Pregnancy 38 weeks	Postnatal (weeks)				SEM
		2	6	12	24	
End-systolic dimension (cm)	3·22	3·30	3·23	3·22	3·17	0·03
End-diastolic dimension (cm)	4·86	4·75*	4·72**	4·68***	4·67***	0·03
Left atrial dimension (cm)	3·74	3·42***	3·45***	3·36***	3·33***	0·06
Total LV wall thickness (cm)	2·01	1·97	1·94	1·81***	1·69***	0·03
LV mass (g)	203	191***	182***	167***	157***	4
Peak LV dD/dt (cm/s)						
Systole	9·3	7·2***	7·0***	6·8***	6·7***	0·3
Diastole	14·1	11·3*	12·0	11·5*	11·3*	0·8
Ejection fraction (%)	70	67***	68***	67***	67***	2
Mean Vcf (Diam/s)	1·27	1·09***	1·08***	1·05**	1·07***	0·02

Values quoted are means. The standard error of the mean (SEM) was determined from the analysis of variance and was based on the intra-patient variability.

P (probability) values indicate significant differences from values at the end of pregnancy; $^{*}P<0·05$, $^{**}P<0·01$, $^{***}P<0·001$

LV, Left ventricular; dD/dt, rate of change of dimension; Vcf, rate of circumferential fibre shortening

Table 4. Haematological and blood pressure results

	Pregnancy 38 weeks	Postnatal (weeks) 2	6	12	24	SEM
Haemoglobin (g/dl)	12·0	12·4*	12·6***	12·7***		0·1
Haematocrit (%)	33·8	37·6***	38·4***	37·8***		0·5
Blood pressure (mmHg)						
Systolic	102	101	100	98	109**	2
Diastolic	63	65	63	64	69**	1

Values quoted are means. The standard error of the mean (SEM) was determined from the analysis of variance and was based on the intra-patient variability.

P (probability) values indicate significant differences from values at the end of pregnancy; $^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}01$, $^{***}P<0{\cdot}001$.

pliance or distensibility, was also significantly reduced postnatally.

Haematological and blood pressure measurements are shown in Table 4. Haemoglobin and haematocrit were both significantly increased by 2 weeks after delivery and thereafter showed no further significant changes. Systolic and diastolic blood pressures did not change significantly over the first 12 weeks after delivery but then both increased between 12 and 24 weeks to values significantly greater than those recorded at the end of pregnancy.

A comparison of the haemodynamic measurements between lactating and non-lactating mothers revealed no significant differences in any of the variables at any of the time points studied.

Table 5 compares the haemodynamic results obtained 24 weeks after delivery with those found in the age-matched control group. Stroke volume was higher in the postnatal group, although this was only significant for the aortic and mitral sites. This increase was associated with significant increases in aortic and pulmonary arterial areas. Heart rate and cardiac output did not differ significantly between the two groups. Left ventricular wall thickness and mass were significantly greater in the postnatal group but the indices of ventricular contractility were significantly decreased.

Discussion

There have been few reports describing the use of Doppler ultrasound for the measurement of maternal cardiac output in late pregnancy. James *et al.* (1984) measured cardiac output during elective caesarean section in 16 subjects. Aortic velocities were measured using continuous wave Doppler and aortic diameter was measured using A-mode echocardiography. Cardiac output was found to be 6·9 l/min (SD 1·0) pre-operatively and there was no significant difference 24 h after delivery. Using similar methods the same group measured cardiac output in seven pregnant subjects and again more than 4 weeks after delivery (James *et al.* 1985). The only results quoted were the percentage changes in cardiac output and the only significant difference was a decrease in cardiac output between 25–28 weeks gestation and after delivery. More recently Easterling *et al.* (1986) measured Doppler aortic flow in 18 normal women in the third trimester. They reported a mean cardiac output of 6·6 l/min (SD 1·8 l/min), which is slightly lower than but not significantly different from the results reported here.

Haites *et al.* (1985) measured velocities in the aortic arch during pregnancy using continuous wave Doppler ultrasound. They reported the aortic velocity integral (VI) to be 33·4 cm at a mean gestation of 19 weeks compared with 23·4 cm in age-matched non-pregnant controls (an increase of 43%). The same group recently reported a longitudinal study of aortic VI and minute distance (VI×HR) in the left lateral position during pregnancy and compared measurements with a group of non-pregnant controls (McLennan *et al.* 1987). Aortic VI increased from a non-pregnant mean of about 29 cm to a maximum of about 34 cm at 16 weeks gestation (an increase of only 19·7%). Thereafter VI decreased and by term there was no significant difference compared with non-pregnant values. During the first week after delivery there were significant increases in VI, HR and minute distance but by 6 weeks these measurements had returned to non-pregnant control values. There

Table 5. Comparison of postnatal (24 weeks) and control results

	Postnatal $n = 15$	Control $n = 15$	Probability
Heart rate (beats/min)	69 (8)	73 (6)	NS
Left ventricular ejection time (ms)	296 (12)	290 (12)	NS
Area (cm^2)			
Aortic	3·97 (0·34)	3·67 (0·30)	<0·05
Pulmonary artery	6·61 (0·35)	6·24 (0·44)	<0·05
Mitral valve	6·69 (0·47)	6·36 (0·41)	NS
Velocity integral (cm)			
Aortic	18·4 (1·5)	18·5 (1·2)	NS
Pulmonary	10·6 (0·8)	10·8 (1·1)	NS
Mitral	10·8 (1·1)	10·4 (1·0)	NS
Stroke volume (ml)			
Aortic	73·4 (7·5)	66·9 (5·9)	<0·05
Pulmonary	70·3 (8·2)	66·6 (5·9)	NS
Mitral	72·5 (8·9)	65·6 (5·5)	<0·05
Cardiac output (l/min)			
Aortic	5·02 (0·50)	4·92 (0·35)	NS
Pulmonary	4·93 (0·55)	4·95 (0·37)	NS
Mitral	4·93 (0·59)	4·90 (0·46)	NS
End systolic dimension (cm)	3·17 (0·28)	2·99 (0·28)	NS
End diastolic dimension (cm)	4·67 (0·32)	4·51 (0·20)	NS
Total LV wall thickness (cm)	1·69 (0·15)	1·54 (0·15)	<0·05
Left atrial dimension (cm)	3·33 (0·36)	3·19 (0·26)	NS
Peak LV dD/dt (cm/s)			
Systole	6·7 (1·1)	7·6 (0·9)	<0·05
Diastole	11·3 (2·6)	11·9 (1·2)	NS
Ejection fraction (%)	67 (4)	70 (4)	<0·05
Mean Vcf (Diam/s)	1·07 (0·09)	1·16 (0·12)	<0·05
LV mass (g)	156 (37)	129 (23)	<0·05
Blood pressure (mmHg)			
Systolic	109 (5)	105 (7)	NS
Diastolic	69 (7)	65 (7)	NS

Results are mean (SD) values.

LV, Left ventricular; dD/dt, rate of change of dimension; Vcf, rate of circumferential fibre shortening; NS, not significant.

appears to have been a fall in minute distance but no change in VI between the end of pregnancy and 6 weeks after delivery but the significance of these changes was not reported. The differences in VI detected by these workers and those found in the present study are difficult to explain. Information about the normal non-pregnant aortic VI is extremely scarce. Gisvold & Brubakk (1982) reported the mean aortic VI in a group of women aged 20–40 to be 19·2 cm and Gardin *et al.* (1984) studied men and women, between 20 and 33 years of age, and reported a mean of 19 cm. Our non-pregnant data are comparable with these results and suggest the possibility of a systematic overestimation of VI by Haites *et al.* (1985) and McLennan *et al.* (1987).

The present study is the first to measure cardiac output systematically throughout the puerperium and provides strong evidence to suggest that many of the haemodynamic readjustments which occur after delivery are complete by 2 weeks.

Previous serial studies measuring cardiac output at the end of pregnancy and after delivery are shown in Table 6. Only Katz *et al.* (1978) and Maruta (1982) reported a decrease in serial measurements of SV and cardiac output after delivery. The decreases in HR (22%), SV (19%) and cardiac output (37%) at 6–12 weeks after delivery, reported by Katz *et al.* (1978), are similar to our results. Maruta (1982) found decreases in HR, SV and cardiac output of 15%, 7% and 20%, respectively, 1–2 weeks after

Table 6. Previous serial studies of cardiac output during pregnancy and the puerperium

Author	Position	Method	Time of PN study	End of pregnancy SV	End of pregnancy HR	End of pregnancy CO	Postnatal SV	Postnatal HR	Postnatal CO	Per cent change SV	Per cent change HR	Per cent change CO
Roy (1966)*	S	Dye	?	73	78	5·80	77	72	5·50	+5	−8	−5
Walters (1966)*	?	Dye	2–17 weeks	79	79	6·19	80	72	5·27	+1	−9	−15
Ueland (1969)†	L	Dye	6–8 weeks	69	83	5·70	71	70	5·00	+3	−16	−12
	S	Dye	6–8 weeks	52	86	4·50	73	70	5·10	+40	−19	+13
Katz (1978)†	L	M-M	6–12 weeks	97	88	8·56	79	69	5·40	−19	−22	−37
Atkins‡ (1981)†	L	IC	6 weeks	79	76	5·80	93	57	5·40	+18	−25	−7
	L		4–16 months				103	64	6·60	+30	−16	+14
Myhrman (1982)†	L	IC	6–25 weeks	78	68	5·30	84	61	5·10	+8	−10	−4
Maruta (1982)	S	M-M	1–2 weeks	74	84	6·14	69	71	4·93	−7	−15	−20
Present study§	L	Dop	2 weeks	88	87	7·60	81	69	5·56	−8	−21	−27
	L	Dop	6 weeks				80	67	5·35	−9	−23	−30
	L	Dop	24 weeks				73	69	5·02	−17	−21	−34

PN, Postnatal; SV, stroke volume, HR, heart rate, CO, cardiac output; S, supine; L, lateral; ?, undefined; Dye, dye dilution, M-M, M-mode echocardiography; IC, impedance cardiography; Dop, combined cross-sectional and Doppler echocardiography

*Partly serial study, †serial study; ‡data are taken from graphs; §aortic results only.

delivery, slightly less than those found in our study (21%, 8–10% and 26–28% respectively). Rubler *et al.* (1977) compared values at term in the left lateral position, with those in non-pregnant controls and found decreases of 20%, 20% and 33% in SV, HR, and cardiac output respectively.

It is clear from Table 6 that the reported values of HR and SV varied considerably, even in patients in the same position. These differences may partly be explained by the different investigative techniques. Atkins *et al.* (1981) measured cardiac output by impedance cardiography in a group of eight women at 6 weeks and then again at 4–16 months after delivery. They reported a 25% decrease in HR at 6 weeks followed by an increase to near prepregnancy levels. Stroke volume, which was increased by 18% at 6 weeks then increased further to 103 ml at 4–16 months (amounting to a total increase of 30% relative to the end of pregnancy). The net result in cardiac output was a 7% fall at 6 weeks and a 14% increase at 4–16 months. While this was a well constructed serial study, the results must be viewed with some caution as the method is based on a number of assumptions that may not be applicable throughout pregnancy (de Swiet & Talbert 1986). Certainly the values of SV and cardiac output recorded at 4–16 months after delivery are considerably higher than accepted normal values (Barratt-Boyes & Wood 1958; Kennedy *et al.* 1966). Calculation of SV from M-mode derived diastolic and systolic ventricular volumes will theoretically overestimate SV at high end-diastolic volumes (Fortuin *et al.* 1971). This may explain the higher SVs reported by Katz *et al.* (1978) at the end of pregnancy, but does not account for the significantly smaller SV found by Maruta (1982) at the same gestation, using the same technique.

End-diastolic and left atrial dimensions decreased significantly after delivery; these findings have been reported previously (Katz *et al.* 1978; Rubler *et al.* 1977) The size of the decrease is similar in all three studies (4–6% for end-diastolic dimension and 8–11% for left atrial dimension). These findings suggest an increased venous return consistent with the well documented increase in circulating volume during pregnancy (Hytten & Paintin 1963). A close approximation of end-diastolic volume (EDV) and end-systolic volume (ESV) can be obtained by cubing the respective dimensions (Feigenbaum *et al.* 1969; Murray *et al.* 1972). Rubler *et al.* (1977), Katz *et al.* (1978) and Maruta (1982) all used this method to calculate SV (EDV–ESV). If the dimensions obtained in the present study are used to calculate SV using this formula the results are: 81 ml at 38 weeks and 70 ml at 24 weeks after delivery. This represents a decrease of 14% which is very similar to the decrease in SV determined by the Doppler method.

In the present study aortic, pulmonary artery and mitral orifice areas were all found to be significantly increased at the end of pregnancy. Katz *et al.* (1978) measured aortic root diameter using M-mode echocardiography; their values were consistently larger than our results, but the change in aortic area was of similar order to that found in the present study (−14% *v.* −11%). This discrepancy may be due to the measurement of aortic diameter at different sites. Diameters measured at the aortic root are considerably larger than those measured at the aortic orifice (Ihlen *et al.* 1984). Since flows calculated using areas obtained at the orifice correlate best with invasively determined flows (Ihlen *et al.* 1984) this site was chosen for the present study. Recently Hart *et al.* (1986), using a similar technique to Katz *et al.* (1978), reported a change in aortic area from 4·56 cm^2m^{-2} at the end of pregnancy to 3·49 cm^2m^{-2} 3–6 months postpartum, a decrease of 23%. It is interesting to note that these authors found a much smaller decrease in aortic area in primigravidae (8%), who make up the majority of the present study population.

No data are available regarding changes in pulmonary artery and mitral orifice areas during pregnancy. However Limacher *et al.* (1985) reported a significant increase in tricuspid annulus diameter as well as right atrial and ventricular dimensions during pregnancy. It would appear therefore that dilatation involves not only all the intracardiac chambers but their respective outflow valves as well. Some of these changes are likely to be due to the increased circulating volume already mentioned but there is also evidence that structural changes occur in the aorta during pregnancy (Manolo-Estrella & Barker 1967). These may be related to alterations in sex steroid levels; oestrogen receptor sites are known to be present in primate aortic tissue (McGill & Sheridan 1981) and oestrogen has been shown to alter collagen biosynthesis (Beldekas *et al.* 1981).

The evidence concerning myocardial hypertrophy during pregnancy is contradictory. A number of electrocardiographic studies have failed to show any electrical evidence of hypertrophy (Zatuchni 1951; Carruth *et al.* 1981). Kuzniar *et al.* (1983), using M-mode echocardiography, reported a significant increase in inter-ventricular septal dimension during the third trimester. Other studies using M-mode have failed to confirm these findings (Sanchez *et al.* 1986; Rubler *et al.* 1977; Katz *et al.* 1978). The present study demonstrated a significant increase in total left ventricular wall thickness and confirms the increase in M-mode derived left ventricular mass previously reported by Katz *et al.* (1978). Estimates of ventricular mass using this method have been shown to correlate quite closely with postmortem anatomical ventricular mass (Devereux & Reichek 1977). Serial measurements of wall thickness, however, have to be interpreted with caution because of the relatively large measurement variability associated with measuring small dimensions (Monoson *et al.* 1978).

Left ventricular hypertrophy in response to prolonged physical training is well recognized (Rost 1982). Recently, increases in left ventricular wall thickness and mass of a similar magnitude to those reported in the present study have been reported in young freshman athletes after a period of only 10–12 weeks physical training (Lusiani *et al.* 1986). It is perhaps not surprising, therefore, in view of the considerably increased workload on the heart, that some degree of hypertrophy occurs during pregnancy.

All the indices of myocardial contractility showed a significant decrease by 2 weeks after delivery and thereafter showed no further significant changes. Rubler *et al.* (1977) compared measurements of ejection fraction and mean Vcf in the third trimester with those in a group of non-pregnant controls. They found values significantly higher in the pregnancy group, the differences being similar to those reported here. Katz *et al.* (1978) reported a decline in both of these values after delivery although neither reached significance. Maruta (1982) reported a 6% fall in ejection fraction and a 13% fall in mean rate of circumferential fibre shortening (Vcf) at 2 weeks after delivery. These changes are similar to those reported in the present study (4% and 14% respectively). Systolic time intervals have also been used to assess changes in contractility. Increases in isovolumic contraction time (Rubler *et al.* 1973) and pre-ejection period (Cellina *et al.* 1983; Kagiya *et al.* 1984) have similarly suggested a decline in contractility after delivery. This alteration in contractility may be secondary to a decreased end-diastolic volume (Frank-Starling Principle) or to the rapid decline in circulating oestrogens, which may affect the myocardium directly (Tanz 1963).

Serial data on blood pressure changes in the puerperium are surprisingly sparse. Most of the work has been done on small numbers of subjects and isolated postnatal measurements have been made at 6–12 weeks. Some authors have found a slight increase in systolic BP (MacGillivray *et al.* 1969; Katz *et al.* 1978), others have found a slight decrease (Ihrman 1960; Atkins *et al.* 1981; Myhrman *et al.* 1982). Diastolic BP has generally been reported to fall slightly (Ihrman 1960; MacGillivray *et al* 1969; Myhrman *et al.* 1982), although Katz *et al.* (1978) demonstrated a significant elevation at 6–12 weeks. We found no significant changes in either systolic or diastolic BP between 38 weeks and 12 weeks post delivery. The significant increase in both systolic and diastolic pressure between 12 and 24 weeks is unexplained. The increase did not appear to be related to lactation nor to the type of contraception used.

Finally this study suggests that some of the haemodynamic changes associated with pregnancy have not completely regressed 24 weeks after delivery. Left ventricular wall thickness and mass were significantly greater than in a control group suggesting an element of residual hypertrophy. There was also evidence of residual dilatation of the semilunar valves, which accounts for the slightly higher stroke volumes measured at these sites in the postnatal group. Perhaps more surprisingly all the indices of ventricular contractility were significantly lower in the postnatal group. Our control data agree closely with the non-pregnant data reported by Rubler *et al.* (1977) suggesting this may represent a true diminution in myocardial function. Although these findings are very interesting the differences between the groups were small and probably of little clinical significance.

Acknowledgments

The work was supported by a grant from Newcastle Area Health Authority. We would like to thank Dr Alan Murray for his methodological advice.

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Received 27 October 1986
Accepted 25 June 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1040–1044

Inhibition of uterine contractions of premature labour with an oxytocin analogue. Results from a pilot study

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Summary. A competitive inhibitor of the action of oxytocin on the uterus, 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin, was studied for the first time in 13 patients with established, uncomplicated premature labour. Intravenous infusion of 10–100 μg/min of the analogue was given for 1–10 h and the effect was monitored by external cardiotocography. In all women an inhibition of uterine activity was observed, and in the majority of patients infused with 25 μg/min and a total dose of about 5 mg or more of the drug total inhibition of uterine contractions was achieved. There were no effects on the maternal and fetal pulse rates, nor were there any other side-effects. The results of this preliminary study support the concept of an increased concentration of uterine oxytocin receptors being aetiologically important in uncomplicated premature labour. They also suggest that the present oxytocin antagonist could be an interesting therapeutic alternative in the condition, primarily because of the marked selectivity of its effect.

The mechanism of premature labour is in most cases unclear. This has lead to the use of a variety of non-specific therapies, e.g. ethanol, β_2-adrenoceptor stimulants, prostaglandin synthesis inhibitors, calcium antagonists and magnesium sulphate. All of these substances have potentially severe maternal and fetal side-effects. Recently, oxytocin and/or uterine oxytocin receptors have been ascribed aetiological roles for the uterine hyperactivity in premature labour (Fuchs *et al.* 1982). To study further the importance of the hormone in this condition and to develop a more selective tocolytic agent, a series of competitive inhibitors of the uterine action of the posterior pituitary hormones were synthesized (Melin *et al.* 1986). The most effective antagonist was found to be 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin, both *in vitro* on human myometrial strips (Åkerlund *et al.* 1985) and *in vivo* on vasopressin-stimulated uterine contractions in non-pregnant women (Åkerlund *et al.* 1986). This analogue also had a prolonged plasma half-life in comparison with oxytocin (Lundin *et al.* 1986). We report results from the first experiments with this oxytocin analogue on uterine contractions of premature labour in a joint Swedish–Danish study.

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Patients and methods

Women in premature labour at between 27 and 35 completed weeks gestation were studied with external cardiotocographic recordings (Hewlett–Packard 8030A or Corometric Cardiotocograph 111A). The inclusion criteria for the study were regular uterine contractions with a frequency of ≥4/20 min, persisting after 2 h of bed rest, and a Westin cervical score of between 3 and 6 (Gentz *et al.* 1983); this is a modified Bishop score ranging from 0 to 10 which includes dilatation, effacement, station, consistency and position of the cervix. Furthermore, patients were only included if a continuous and clear external recording of contractions could be obtained. Patients with placental abruption, moderate or heavy vaginal bleeding, signs of chorioamnionitis, rupture of the membranes, severe pre-eclampsia and with malformations of the uterus or the fetus were excluded.

Altogether 13 women participated in the study with an intravenous infusion of 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin (Ferring AB, Sweden) in 5·5% glucose. The doses of the drug and the durations of treatment in the different patients were increased during the study, as more experience was gained, so that the maximal infusion rates varied between 10 and 100 μg/min, and the duration of treatment and total dose varied between approximately 1 and 10 h and 1·5 and 54 mg, respectively

The external uterine activity recordings were quantified by the same person in terms of frequency of contractions in 20-min periods.

Approval for the study was obtained from the local ethics committees and from the Swedish and Danish National Boards for Health and Welfare.

Results

Table 1 shows a summary of the clinical data of the participating patients and the effects of different doses of 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin on the frequency of uterine contractions. An individual recording from one of the patients is illustrated in Fig. 1. In all patients infused with ≥25 μg/min of the drug a marked inhibition of uterine contractions was observed, and in 6 of the 7 patients receiving a total dose of ≥4·7 mg there was a total inhibition of contractions. All patients reported that the uterine contractions decreased concomitant with drug administration. No palpitation, tremor or other side-effects were observed. The blood pressure and pulse rate of the mother did not change, and the fetal heart rate was unaffected (Fig 1)

Table 1. Summaries of clinical data, treatment with 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin infusion and the effect on the frequency of uterine contractions in patients with premature labour

	Clinical data			Treatment			No of contractions /20 min	
Patient	Parity	Gestational age (weeks)	Cervical score at the start of treatment	Duration	Maximal infusion rate (μg/min)	Total dose (mg)	Before start of treatment	At maximal effect
1	0	34	4	2 h 40 min	10	1·6	7	4
2	2	36	4	1 h 35 min	20	1·5	5	3
3	0	33	5	1 h 20 min	50	3·0	5	2
4	1	34	6	1 h 5 min	50	3·3	5	2
5	0	34	3–4	1 h 40 min	50	4·0	4	1
6	0	34	4	1 h 45 min	50	4·5	6	1
7	1	35	4–5	2 h	50	4·7	9	0
8	0	28	6	3 h 40 min	25	5·3	9	0
9	0	35	4	2 h 15 min	50	6·8	4	2
10	0	32	6	7 h	50	12·2	9	0
11	3	35	6	5 h 25 min	50	16·3	5	0
12	0	33	6	7 h	100	30·4	5	0
13	0	34	7	9 h 40 min	100	53·8	7	0

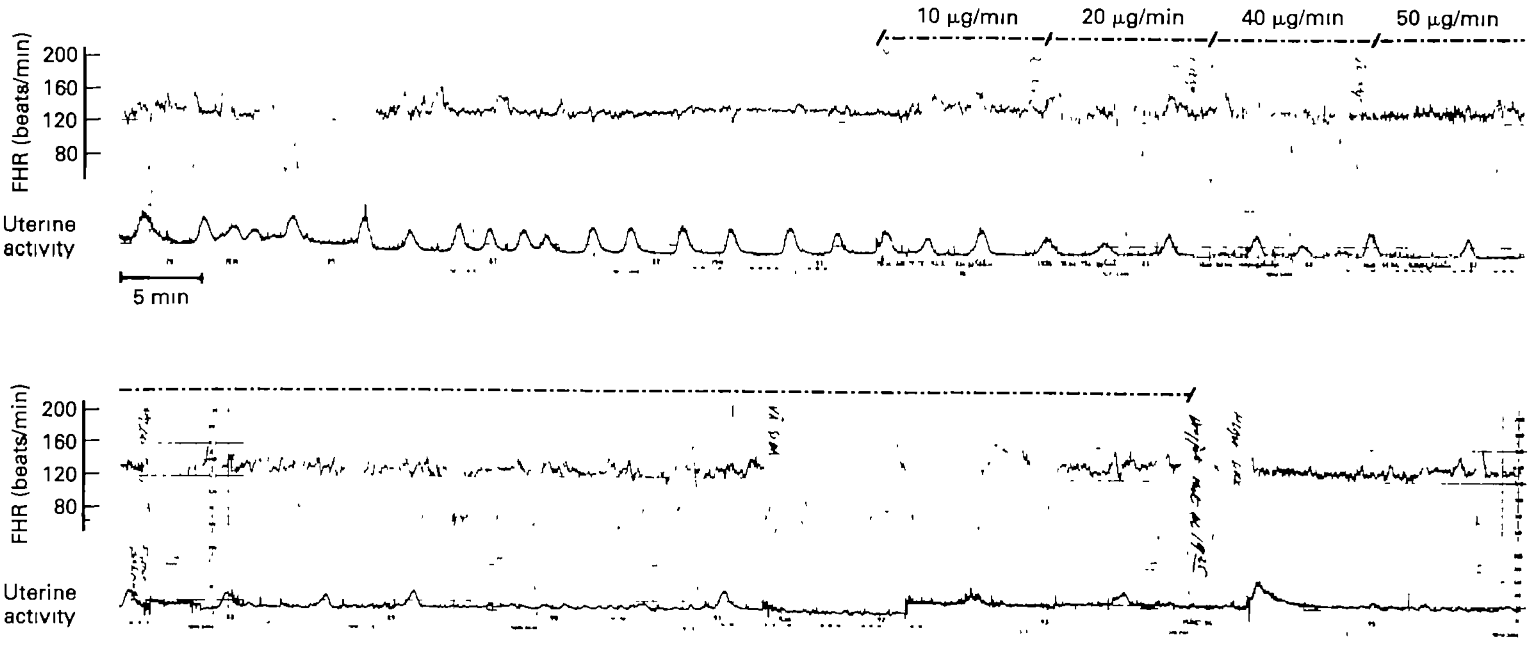

Fig. 1. The effect of intravenous infusion of 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin (dotted line) in a woman with preterm labour at 33 weeks gestation and a Westin cervical score (modified Bishop score) of 4.

Seven patients were given additional therapy with the β_2-adrenoceptor stimulator terbutalin (Swedish part of the study) at 1–3 days after the analogue infusion because of recurrent labour In spite of this, two of them were delivered prematurely at 35 weeks gestation, 1 and 2 weeks after the analogue infusion. Three of the patients were given prophylactic oral ritodrine treatment for 1 week after the analogue infusion (Danish part of the study) but in spite of this one of them was delivered after premature labour at 33 weeks gestation, 6 weeks after the analogue infusion. All other patients reached at least 36 completed weeks gestation. No complication of labour or subsequent breast feeding was observed.

Discussion

Premature labour is still a serious problem causing a significant part of the mortality and morbidity of the newborn. In some cases, such as placental abruption or intrauterine infection, tocolytic treatment is contraindicated (Tejani & Venna 1983), but in uncomplicated cases inhibition of the uterine hyperactivity, even for a limited period, could be of great value at a critical time of pregnancy (Editorial 1979). The most commonly used tocolytic drugs, β_2-adrenoceptor stimulants, exert their effect by increasing the intracellular content of cyclic AMP in all tissues with β_2-adrenoceptors. Thus, these substances cause not only tocolysis but often significant side-effects including tachycardia in mother and fetus, shortness of breath, pulmonary oedema, tremor, nausea, vomiting and a diabetogenic effect. Consequently, the side-effects rather than the optimal tocolytic effect are usually limiting.

Recently, Fuchs & Fuchs (1984) suggested that an increase in the number of oxytocin receptors of the myometrium may be an important factor in the initiation of labour, sensitizing the uterus even to normal concentrations of circulating oxytocin. An increase in the oxytocin receptor content has also been associated with premature labour (Fuchs *et al.* 1982). In fact, patients with this condition had oxytocin receptor concentrations as high as patients in early labour at term (Fuchs *et al.* 1984). Thus, there is reason to believe that a selective blockade of the oxytocin receptors could be an adequate way of treating preterm labour. Such therapy should also cause minimal side-effects since the uterus and the breasts are the only known major target organs for oxytocin.

Clinical assessment of a tocolytic substance in premature labour is technically difficult since uterine contractions can only be recorded externally. In the present study only patients who could endure continuous recording and who were sufficiently slim to give a technically acceptable tracing could be included. Furthermore, the diagnosis of premature labour is difficult since the spontaneous resolution of premature uterine hyperactivity is common. Therefore, none of the patients in the present study received treatment with the oxytocin analogue within the first 2–3 h after admission. The genuineness of the premature labour in our patients is also supported by the fact that the status of the cervix in all of the patients was clearly affected and that several of them required additional treatment with β_2-adrenoceptor stimulating drugs because of recurrent premature labour after the analogue infusion was stopped.

In the present initial clinical study of 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin only open trials and only one infusion session of limited size and duration per patient were permitted. However, in the majority of the patients infused with 25 μg/min and a total dose of at least 5 mg, total inhibition of the uterine contractions was achieved. The treatment appeared to be highly selective since no side-effects occurred.

The results of the present study support the concept of an increased concentration of oxytocin receptors being aetiologically important in uncomplicated premature labour, as the tocolytic effect was presumably due to competitive binding of the analogue to oxytocin receptors (Åkerlund *et al.* 1985; Melin *et al.* 1986). Since this pilot study has revealed no unexpected side-effects, further trials on an enlarged number of patients uniformally treated and a double-blind comparison with one of the presently used β-mimetics can be initiated.

Acknowledgments

The skilful technical assistance of A.–M. Carlsson is gratefully acknowledged. The authors were supported by grants from the Swedish Medical Research Council (no B87-17X-06571-05B) and Lund University.

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Received 17 November 1986
Accepted 2 February 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol 94, pp. 1045–1051

Effect of relaxin on prostaglandin E production by human amnion: changes in relation to the onset of labour

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Summary. The effect of relaxin on prostaglandin E (PGE) production by human amnion *in vitro* was investigated. When amniotic discs were incubated in the presence of increasing concentrations of relaxin, two distinct effects were observed. Discs prepared from women delivered by caesarean section before the onset of labour showed a significant decrease in PGE output at relaxin concentrations of 0·5–2 μg/ml; the effect was abolished at higher relaxin concentrations. Discs obtained from women delivered after labour of spontaneous onset responded to the addition of relaxin (4–8 μg/ml) with a significant increase in PGE output, although this increase was only evident in patients in whom labour had started with intact membranes. These results suggest that relaxin, which is present in decidua and chorion laeve at term, may have a paracrine effect on the amnion, inhibiting PGE production during continuing pregnancy but favouring its production during spontaneous labour.

Although the mechanism responsible for the onset and maintenance of human parturition remains poorly understood, prostaglandins (PG) play a prominent role (Liggins *et al.* 1977; Keirse 1979; Turnbull 1983). The fetal membranes, especially the amnion, are thought to be the site of the increased PG production associated with parturition (Keirse 1979; Casey & MacDonald 1986). These tissues produce relatively large amounts of PGE (Kinoshita *et al.* 1977; Mitchell *et al.* 1978) which can bind to specific receptors in the uterus (Wakeling & Wyngarden 1974; Adelantado *et al.* 1985) and can cause myometrial contractility and cervical ripening (Karim *et al.* 1970; MacKenzie & Embrey 1977). Hence, the factors regulating PGE production in the fetal membranes are potentially very important in relation to the onset and maintenance of spontaneous labour.

Relaxin is present in maternal plasma during pregnancy, but the levels show no consistent changes towards term (Eddie *et al.* 1986). An intrauterine source of relaxin has been demonstrated: it has been isolated from cultured human decidua and placental basal plate (Bigazzi *et al.* 1980; Yamamoto *et al.* 1981; Fields & Larkin 1981) and localized immunohistochemically in the decidua and the cytotrophoblast of the chorion laeve (Koay *et al.*

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1985). A paracrine action of choriodecidual relaxin has been suggested by the demonstration of specific receptors in amnion and chorion (Koay *et al.* 1986) and by the increased production of plasminogen activator and collagenase activity by these tissues in response to relaxin *in vitro* (Koay *et al.* 1986). Thus, relaxin may be one of the hormones involved in promoting collagenolytic activity in the fetal membranes, leading to their weakening and rupture near term.

Since the amnion is a major intrauterine source of PGE and since relaxin may reach this tissue from the neighbouring choriodecidua, we have investigated the effect of purified relaxin on the rate of PGE production by amnion *in vitro.*

Materials and methods

Fetal membranes were obtained immediately after delivery from two groups of women:

Group 1 included six women delivered at term by elective caesarean section before the onset of labour. Operative delivery was indicated because of previous caesarean section or malpresentation such as shoulder or breech presentation. The mean (range) values in this group were 33 (26–40) years for maternal age, 0·8 (0–2) for parity, 38 (37–39) weeks for gestational age and 3308 (2655–4040) g for infant birthweight.

Group 2 included nine women delivered vaginally at term following labour of spontaneous onset. In five of these women cervical dilatation during labour progressed to 4 cm before the membranes were artificially ruptured and none required oxytocin augmentation. Analgesia in labour was provided with epidural block, pethidine or nitrous oxide at the patient's request. Mean maternal age in this group was 26 (18–33) years, parity 0·4 (0–1), gestational age 40 (39–41) weeks and newborn weight 3488 (2780–4639) g.

All women were delivered of healthy singleton infants and there were no fetal or maternal complications during pregnancy.

Preparation of amniotic discs

Strips of fetal membranes were rinsed in 0·15 M NaCl; the amnion was separated from the choriodecidua and placed on a hard plastic mat. Discs of amnion were punched with a 17 mm diameter cork bore and were immersed in pseudo-amniotic fluid (PAF, Schwartz *et al.* 1977) bubbled with 95% O_2 and 5% CO_2.

Incubations were set up in quadruplicate at 37°C in stoppered conical flasks containing 2 ml of pre-gassed PAF±added relaxin and one amniotic disc per flask. At the end of the incubation time, the medium was recovered and the discs were dried to constant weight and stored at −20°C for DNA estimations. Stock solutions of relaxin were prepared fresh on the day of use by dissolving a known weight of lyophilized sequence grade (3000 GPU/mg) porcine relaxin (James *et al.* 1977; Sherwood & O'Byrne 1974) in PAF; dilutions from the stock were used for incubations. Since relaxin in solution can be readily adsorbed on to glass and plastic surfaces, the actual concentration of relaxin in solution was determined by radioimmunoassay (Afele *et al.* 1979). As expected, adsorption was greatest at the lowest relaxin concentrations. In this paper results refer to the actual relaxin concentration in solution.

Prostaglandin E estimations

PGE was measured by radioimmunoassay (Mitchell *et al.* 1978) using an antiserum kindly donated by Dr M. T. Withnall (May & Baker Ltd). The specificity of this antiserum was PGE_2 100%, PGE_1 100%, $PGF_{2\alpha}$ 3·2%, PGA_2 1·2%, PGB_2 and arachidonic acid <0·2%. Results are expressed as PGE because the antiserum does not distinguish between PGE_1 and PGE_2. Aliquots (0·5 ml) of medium were acidified with citric acid and extracted with 2 ml of ethyl acetate. Extraction recoveries ranged between 70 and 85%. Intra-assay and interassay coefficients of variation were 9·5% and 16% respectively. The mean coefficient of variation of quadruplicate estimations (including tissue weighing and assay variations) was 32%.

Lactate estimations

The metabolic activity of the tissue was assessed by measuring the production of lactate (Schwartz *et al.* 1977). Aliquots of medium were acidified with perchloric acid and stored frozen at −20°C. The samples were thawed, neutralized with potassium hydroxide and lactate was estimated by the method of Gutman & Wahlefeld (1974).

DNA estimations

DNA was extracted from the discs by heating at 90°C for 30 min in 0·3 N perchloric acid and was estimated colorimetrically (Burton 1968) using calf thymus DNA (Sigma) of known inorganic phosphate content as standard.

Statistics

Statistical differences were assessed by the Mann–Whitney, Kruskal–Wallis and Friedman tests with the critical range method.

Results

The average DNA content (nmol DNA-Pi per disc) of the discs was 12·5 (SEM 1·6) in the six tissue samples obtained at elective caesarean section and 12·9 (1·3) for the nine tissues obtained after labour of spontaneous onset. On the basis of these results it was assumed that the number of cells per disc was similar in the two groups.

Time course of PGE production

As shown in Fig. 1, the rate of PGE production by amniotic discs was constant for up to 6 h, and this was paralleled by the rate of lactate production. The standard incubation time for most experiments was 2 h.

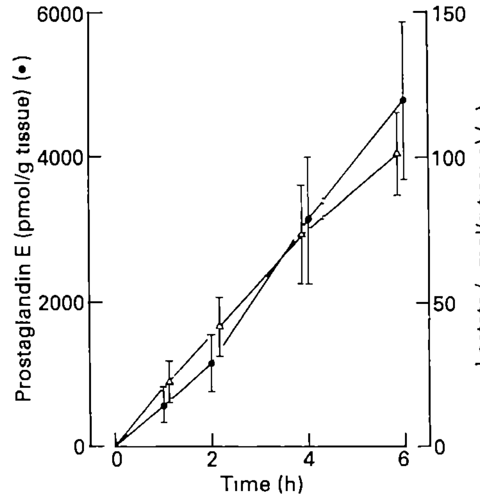

Fig. 1. Time course of prostaglandin E and lactate production by discs of human amnion. Results are the means of three different experiments and the bars represent SEM.

Topographical origin of the discs

The possibility that the rate of PGE production varied in relation to the location of the amnion from which the discs were taken was investigated by comparing the activity of discs punched from areas whose distance from the placental edge was either 2–4 or 14–20 cm. Tissues from four spontaneous labours and one elective section were studied in this way. The mean PGE production rate (pmol/g dry weight per 2 h) in the two areas of amnion was similar: 803 (SEM 196) *v.* 808 (SEM 141). For most experiments discs were punched from areas about 4 cm from the placental edge.

Effects of relaxin on PGE output

The basal individual rates of PGE production are given in Table 1. There was considerable variation between patients, but there were no significant differences between the elective section and spontaneous labour group.

When amniotic discs were incubated in the presence of increasing concentrations of relaxin, two distinct effects were observed. Discs from the elective section group showed a decrease in PGE output (Fig. 2) which was statistically significant (approximately 40% decrease) at relaxin concentrations of 0·5 and 2 μg/ml ($P<0·01$); the effect was abolished at higher relaxin concentrations.

Discs obtained after spontaneous labour responded to the addition of relaxin with a significant increase in PGE output. This increase was dose-dependent and averaged 250% at relaxin concentrations of 8 μg/ml. The stimulating effect of relaxin was accentuated when only patients in whom labour had started with intact membranes were included (Fig. 2) and was statistically significant ($P<0·01$) at relaxin concentrations of 4 μg/ml (234% increase) and 8 μg/ml (354% increase). The changes observed in patients in whom labour started with ruptured membranes were not statistically significant.

Discussion

This paper describes a simple and reproducible way of preparing discs of human amnion which can be maintained in a metabolically active state

Table 1. Prostaglandin E production by amniotic discs incubated at 37°C in pseudo-amniotic fluid

	PGE output (pmol/g dry weight per 2 h)	
	Elective caesarean section	Spontaneous labour
	2751	535
	349	312
	635	685
	712	1000
	1343	223
	1714	268
	—	1230
	—	951
	—	3014
Mean (SEM)	1251 (363)	913 (288)

for several hours. The rate of PGE production by this preparation of amnion is very similar to that described by Mitchell *et al.* (1978), Satoh *et al.* (1981) and Tyson *et al.* (1985) who used superfusion or perifusion techniques. The basal rate of PGE production in tissues obtained at elective caesarean section and those obtained after spontaneous labour was similar; this is in agreement with previous results using whole amnion preparations (Kinoshita *et al.* 1977; Mitchell *et al.* 1978; Satoh *et al.* 1981), but it is interesting to note that the rate of PGE production was higher in dispersed amniotic cells obtained after spontaneous labour than in cells obtained after elective caesarean section (Olson *et al.* 1983; Manzai & Liggins 1984; López Bernal *et al.* 1987).

This study has shown for the first time that relaxin has a direct influence on PGE production by human amnion and can exert both inhibitory and stimulatory effects. Specific receptors for relaxin have been identified in the amnion (Koay *et al.* 1986) and in this tissue relaxin increases the production of plasminogen activator and collagenase activity (Koay *et al* 1986). However, the mechanism by which relaxin can modulate amniotic PG production is not clear.

The different response to relaxin of tissues obtained before and after labour suggests that the effect of this hormone may be dependent on the availability of free arachidonic acid for prostaglandin synthesis. According to Okita *et al.* (1982) arachidonic acid is not liberated from glycerophospholipids in the amnion until early labour. Hence, in tissues obtained at elective caesarean section, the rate of PGE synthesis is likely to be determined primarily by phospholipase (especially phospholipase A_2 and phospholipase C) activity (Bleasdale *et al.* 1983). It is thus possible that relaxin has an inhibitory effect on phospholipase activity in human amnion, as shown with rat myometrial tissue *in vitro* (Williams & El Tahir 1982). The loss of inhibitory activity at high relaxin concentrations could be explained by down regulation of receptor sites or by a superimposed stimulatory effect on the PG synthetase system.

In tissues obtained after labour of spontaneous onset there is increased availability of free arachidonic acid (Okita *et al.* 1982) and the rate of PGE production is dependent on PG synthetase activity (Keirse 1979; Bleasdale *et al* 1983). Hence, it may be postulated that relaxin stimulates the prostaglandin synthetase enzyme system. It is interesting to note that we have demonstrated by immunohistochemical co-localization the presence of relaxin (cytotrophoblast and decidua) and PG syn-

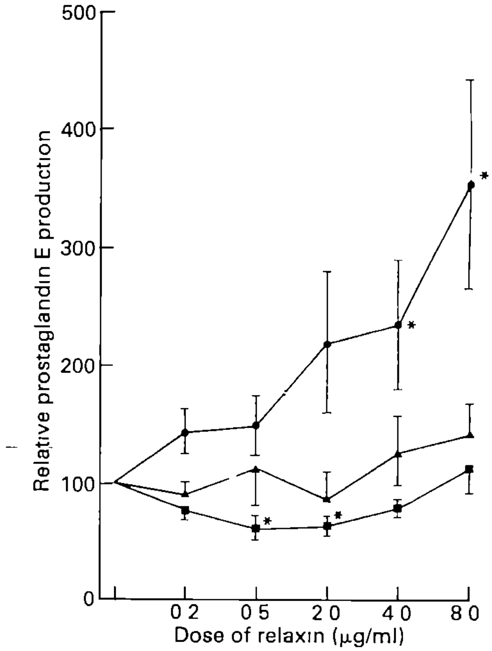

Fig. 2. Effect of relaxin on prostaglandin E production by discs of amnion. Results are means (SEM) and the asterisks indicate values significantly different from controls (no added relaxin). ●, Spontaneous labour (intact membranes) ($n = 5$); ▲, spontaneous labour (ruptured membranes) ($n = 4$); ■, elective caesarean section ($n = 6$).

thetase (amnion, choriodecidua and cytotrophoblast) in tissues obtained at term (Bryant-Greenwood *et al.* 1987). Further experimental work is needed to confirm or refute these hypotheses.

The results from the present study suggest that relaxin of decidual and/or chorionic origin (Bigazzi *et al.* 1980; Yamamoto *et al.* 1981) has a paracrine influence on PGE production in the neighbouring amnion. Whether this effect is related to the biochemical events leading to parturition is presently unknown, but our findings *in vitro* indicate that relaxin may have a dual role *in vivo.* it inhibits intrauterine PG production before the onset of labour; and once the parturitional process has been switched on, it stimulates the release of PG. Furthermore, local administration of relaxin to pregnant women near term has been shown to improve cervical ripening (MacLennan *et al.* 1981; Evans *et al.* 1983).

The apparent lack of effect of relaxin on amniotic tissue obtained from patients in whom labour started with ruptured membranes suggests that these tissues had already responded to endogenous relaxin and were therefore refractory to hormone added *in vitro*. The basal rate of PGE production and the DNA content of these tissues was similar to that of tissues obtained from women whose labour started with intact membranes. It could be argued that high collagenase activity secondary to increased relaxin exposure *in utero* contributed to the early rupture of the membranes in these patients and the amnion had become insensitive to further relaxin stimulation. Moreover, it is possible that the control of prostaglandin production and, perhaps, the onset of labour is different in patients with intact or ruptured membranes.

In recent years several compounds which can influence PGE production in human amnion have been described. These include stimulants such as catecholamines (Di Renzo *et al.* 1984), phospholipids, especially platelet activating factor (Bleasdale & Johnston 1984), extracellular calcium (Olson *et al.* 1983) and other less well characterized factors present in fetal urine (Casey *et al.* 1983). Inhibitory compounds include prolactin (Tyson *et al* 1985), α-fetoprotein (Aussel 1984), phospholipase-inhibitory-proteins (Wilson *et al.* 1985) and other uncharacterized factors present in amniotic fluid (Saeed *et al.* 1982). The findings from the present study confirm that the fetal membranes are target tissues for relaxin and suggest that this peptide may be involved in the complex biochemical control of intrauterine PG production and the physiological onset of labour.

Acknowledgments

This work was supported by Action Research, The National Fund for Research into Crippling Diseases and by the MRC. Professor Gillian Bryant-Greenwood was the holder of a Fogerty Senior Fellowship from NIH.

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Received 30 October 1986
Accepted 3 March 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1052–1058

Steroid conversion and prostaglandin production by chorionic and decidual cells in relation to term and preterm labour

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Summary. The production of progesterone from pregnenolone, of cortisol from cortisone and of prostaglandin E (PGE) under basal and arachidonic acid-stimulated conditions was measured in cells dispersed from chorion and decidua. The cells were obtained after delivery from four groups of women: following spontaneous labour at term (38–42 weeks gestation), at elective caesarean section at term before the onset of labour, after induced labour at term, and after uncomplicated preterm (27–36 weeks) labour. Chorionic cells had a high progesterone output with relatively low cortisol and PGE production, whereas decidual cells had a high cortisol and PGE production rate. Free arachidonic acid stimulated PGE production in both decidual and chorionic cells. There were no significant differences in either steroid or PGE production among the four groups studied. These data suggest that steroid dehydrogenase activity in choriodecidual cells is not related to the mode of onset of labour and that the increased prostaglandin production in intrauterine tissues associated with parturition is due to enhanced availability of arachidonic acid.

The mechanism responsible for human parturition remains unknown, but the fetal membranes and underlying decidua are thought to participate in the endocrine or paracrine activities which might be responsible for the spontaneous onset of labour (Liggins *et al.* 1977; MacDonald *et al.* 1978; Turnbull 1983). The amnion is an important intrauterine site for prostaglandin (PG) production, but has little capacity for steroid conversion (Mitchell *et al.* 1978; Mitchell *et al.* 1982), but the chorionic membrane is able to synthesize progesterone from pregnenolone (Gibb *et al.* 1978) and this activity is also present in decidual cells (Mitchell *et al.* 1982). Decidual cells can synthesize cortisol from cortisone (López Bernal *et al.* 1980) and both decidual and chorionic cells are able to produce prostaglandins, especially PGE (Mitchell *et al.* 1978; Satoh *et al.* 1981; Olson *et al.* 1983) which can cause myometrial contractility and cervical ripening (Karim *et al.* 1970; MacKenzie & Embrey 1977; Ulmsten *et al.* 1983). There is little quantitative information available about the capacity for steroid conversion of chorionic and decidual cells in relation to term and preterm labour, and although the output of PGE by these cells has been measured before and after labour at term (Kinoshita *et al* 1977; Mitchell *et al.* 1978; Olson *et al.* 1983), there is no information on PGE production in relation to uncomplicated preterm labour. We have reported elsewhere (López Bernal *et al.* 1987) on the PGE production rate of amniotic cells in relation to

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spontaneous term and preterm labour, and the purpose of this study was to estimate the capacity for steroid and prostaglandin synthesis of chorionic and decidual cells obtained before and after spontaneous or induced labour at term and after spontaneous preterm labour.

Materials and methods

Fetal membranes were collected from four groups of patients: Group 1 included 13 women in whom labour started spontaneously after 37 weeks gestation (mean 39, range 38–41 weeks). The mean (range) maternal age, parity and newborn weight in this group were: 25 (20–32) years, 0·4 (0–1) and 3289 (2585–3735) g respectively. None of these women received oxytocin in labour and all were delivered vaginally.

Group 2 included nine women delivered by elective caesarean section at 38 (38–39) weeks gestation. Sections were indicated for previous section and/or unfavourable lie or breech presentation and were performed under epidural or general anaesthesia. The mean (range) values in this group were 31 (28–37) years for maternal age, 0·3 (0–1) for parity and 3263 (2970–3535) g for infant birthweight.

Group 3 included six women in whom labour was induced by intravaginal administration of PGE_2 (2·5–5 mg) followed by amniotomy after 3 h. There was no serious fetal or maternal pathology and all patients were delivered vaginally. Mean gestational age was 40 (39–42) weeks, maternal age 30 (21–35) years, parity 0·8 (0–1) and newborn weight 3383 (2545–4070) g.

Group 4 included seven women in whom labour started spontaneously before 37 weeks gestation and who progressed to preterm delivery at a mean 31 (range 27–36) weeks. None of these patients received tocolytic drugs and all were delivered vaginally. Mean maternal age was 24 (16–34) years, parity 0·9 (0–2) and infant birthweight 1619 (784–2705) g.

All women were delivered of healthy singleton infants; analgesia in labour was provided by epidural block, pethidine or nitrous oxide at the patient's request

Preparation of cell suspensions

The chorionic membrane and its attached decidua were separated from the amnion and were rinsed several times in a Krebs-Henseleit solution containing 5 mM glucose and 25 mM Hepes, pH 7·4, (Krebs solution) and kept in ice. The decidua was gently separated from the chorion with a pair of blunt forceps and 0·5 mm slices of both tissues were prepared with a MacIlwain tissue chopper. The slices were weighed and incubated at 37°C for 1 h in Krebs solution (minus Ca^{++}, Mg^{++}) in the presence of 0·5% collagenase (Sigma, type I) and 0·1% hyaluronidase (Boehringer, Mannheim). The resulting cell suspension was filtered through a 170 μm nylon mesh, washed, resuspended in Krebs solution and used for incubations at a concentration of 10^5 cells/ml. Cell viability was assessed by phase contrast microscopy and/or trypan blue staining. Cell suspensions of less than 65% viability were discarded.

Oxygen uptake and lactate estimations

Oxygen consumption was estimated at 37°C in three different cell suspensions containing $0{\cdot}5 \times 10^6$ cells/ml in Krebs solution, with a model 5331 oxygen probe (Yellow Spring Instrument Co., Ohio).

Aliquots of cell suspensions were precipitated with perchloric acid and lactate was measured in the supernatant by the method of Gutman & Wahlefeld (1974).

Steroid and prostaglandin measurements

All incubations were carried out in polypropylene tubes in Krebs solution pre-gassed with 95% O_2 and 5% CO_2 at 37°C. Cell suspensions were incubated alone or in the presence of one of the following substrates: pregnenolone (Sigma) (20 μM), cortisone (Sigma) (100 μM), arachidonic acid (sodium salt, Sigma) (10 μM) Control incubations contained identical additions but cells boiled for 5 min. Under these conditions the substrate concentrations used were optimal for maximal output of the respective products. Unless otherwise specified, all incubations were terminated after 3 h by cooling the tubes at 4°C and centrifuging at about 100 *g* for 10 min; the supernatants were stored at −20°C

Progesterone was estimated by radioimmunoassay (Flint *et al.* 1974) after thin layer chromatography on silica gel (Flint *et al.* 1978). Cortisol was estimated by radioimmunoassay after column chromatography on Sephadex LH-20 (López Bernal *et al.* 1982). PGE was estimated by radioimmunoassay in dilutions of the supernatants without prior extraction or chromatography (Gibson *et al.* 1985). The PGE antiserum was kindly donated by Dr S P. Brennecke and cross-reacted with other prostanoids (Upjohn, Kalamazoo) as follows: PGE_2 100%, PGE 100%, PGA 8%, 6-oxo-PGE 2%, 13, 14-dihydro-PGE 6%, PGA_2 3%, $PGF_{2\alpha}$ 2% 13,14-dihydro-PGE_2 and $PGF_{1\alpha}$ < 1%. The results are expressed as PGE as the antiserum does not distinguish between PGE_1 and PGE_2.

Statistics

The results were assessed by the Kruskal–Wallis and Mann–Whitney tests and were considered significantly different when $P<0{\cdot}05$.

Results

Oxygen consumption and lactate production

For the three cell suspensions, the mean oxygen consumption rate (μmol/10^6 cells per h) of chorionic cells was 0·2 (SD 0·01) and that of decidual cells 0·5 (SD 0·02). Oxygen consumption was not significantly affected by changing the oxygen saturation (20–100%) or by the presence or absence of glucose in the medium.

In the absence of glucose the lactate production rate (μmol/10^6 cells per h) of chorionic and decidual cells was similar : mean 0·09 (SD 0·02); addition of glucose (5 mM) increased lactate production to 0·18 (SD 0·06) in chorionic and to 0·57 (SD 0·11) in decidual cells (n = 3 for each).

Progesterone production from pregnenolone

Both chorionic and decidual cells converted pregnenolone to progesterone in a dose-dependent manner (Fig. 1) and the maximum conversion rate was of the order of 1 nmol/10^6 cells per 3 h. The conversion of pregnenolone to progesterone was inhibited by the specific 3β-hydroxysteroid dehydrogenase inhibitor, epostane (Sterling-Winthrop) (Fig. 1). Comparison between groups (Table 1) showed that the production rate of progesterone was not influenced by the mode of onset of labour at term and was similar in term and preterm labour. Chorionic cells tended to produce more progesterone than decidual cells and this was reversed in cells obtained after preterm labour; however, none of these differences was statistically significant.

Cortisol production from cortisone

Previous work (López Bernal *et al.* 1980) has demonstrated that this activity resides in the decidua and not in the chorion. However, it is difficult to achieve a complete separation between the two tissues and some 11β-hydroxysteroid dehydrogenase activity (up to 20% of the activity of decidual cells) was present in our chorionic cell suspensions (Table 1). The maximum cortisol production rate in decidual cells was of the order of 1 nmol/10^6 cells per 3 h. Cortisol output tended to be highest in cells obtained at elective caesarean section and lowest in cells obtained after spontaneous labour at term (Table 1), although these differences were not statistically significant.

Prostaglandin E production

As shown in Fig. 2, both chorionic and decidual cells released PGE under basal conditions and responded to arachidonic acid with a significant increase in PGE output The net PGE production rate of decidual cells was significantly higher than that of chorionic cells both under basal and arachidonic acid-stimulated conditions (Table 1); there were no statistically significant differences between any of the groups studied (Table 1).

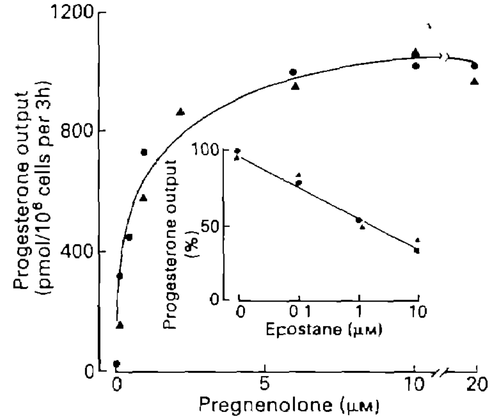

Fig. 1. Progesterone production by term chorionic and decidual cells as a function of pregnenolone concentration The inset represents the effect of the 3β-hydroxysteroid dehydrogenase inhibitor epostane. ●, Decidua, ▲, chorion See text for description of incubations

Table 1. Steroid conversion and prostaglandin E production by chorionic and decidual cells

Substrate	Product (pmol/10⁶ cells per 3 h)		Spontaneous labour ($n = 13$)	Elective caesarean section ($n = 9$)	Induced labour ($n = 6$)	Preterm labour ($n = 7$)
Pregnenolone (20 μM)	Progesterone	Ch	1640 (490)	1431 (447)	1634 (659)	1101 (386)
		De	751 (202)	932 (319)	1171 (289)	1581 (568)
Cortisone (100 μM)	Cortisol	Ch	199 (39)	463 (106)	209 (35)	337 (83)
		De	918 (184)	2362 (710)	1161 (105)	1651 (667)
None	Prostaglandin E	Ch	4·7 (1·3)	6·3 (1·5)	4·3 (1·7)	7·2 (3·1)
		De	8·3 (2·2)	11·2 (3·1)	9·6 (1·9)	10·2 (2·6)
Arachidonic acid (10 μM)	Prostaglandin E	Ch	28·8 (8·0)	36·2 (3·8)	26·2 (7·5)	25·3 (4·1)
		De	33·4 (6·9)	49·8 (4·4)	38·5 (3·5)	46·0 (6·3)

Results are means (SEM) values.
Ch, Chorion; De, decidua.

Discussion

This study has demonstrated that chorionic and decidual cells have a high capacity for steroid conversion and has confirmed that the choriodecidua is an important intrauterine site for PGE production (Kinoshita *et al.* 1977; Mitchell *et al.* 1978). Under our conditions, steroid dehydrogenase activity with both pregnenolone and cortisone as substrates was of the order of 1 nmol/10⁶ cells per 3 h. Decidual cells had similar 3β- and 11β-HSD activities whereas chorionic cells showed preferentially 3β-HSD activity. This was expected because previous studies, using histochemical techniques and fetal membranes from dichorionic twins, have shown that 3β-HSD is a true chorionic enzyme (Mitchell & Powell 1984; Gibb *et al.* 1985), but 11β-HSD resides only in the decidua (López Bernal *et al.* 1980). On the basis of the cortisol production rates we can estimate that our chorionic cells had about 20% contamination by decidual cells, and the same degree of contamination by chorionic cells is likely to have occurred in the decidual cell suspensions.

The capacity for PGE synthesis of chorionic and decidual cells was almost two orders of magnitude lower than the capacity for steroid conversion. Nevertheless, while the capacity for steroid release of these cells in the absence of substrate was negligible compared to the maximum rate of production, the cells were able to release significant amounts of PGE from endogenous precursors, and in the presence of added arachidonic acid PGE release increased four- to five-fold. PGE binds to specific receptors in the uterus (Wakeling & Wyngarden 1974; Adelantado *et al.* 1985) and can cause myometrial contractility and cervical ripening (Karim *et al.* 1970; MacKenzie & Embrey 1977; Ulmsten *et al.* 1983). Hence, PGE production in intrauterine tissues is potentially very important for the spontaneous onset of labour.

Our PGE production rates in chorionic and decidual cells are very similar to those described by Olson *et al.* (1983) and Skinner & Challis (1985) who used similar methods. These authors found a significant increase in PGE production in decidual but not in chorionic cells obtained after spontaneous labour compared with cells

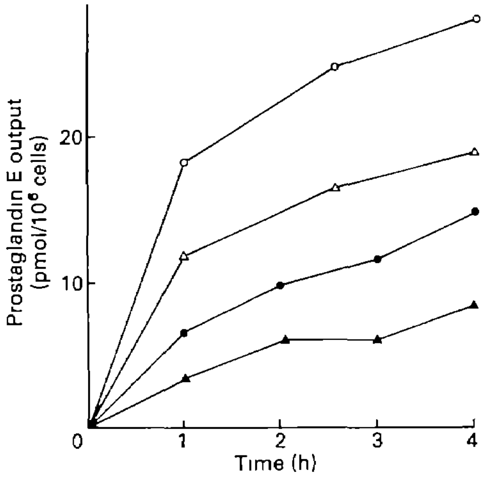

Fig. 2. Time course of prostaglandin E production by term chorionic and decidual cells. Note the increased PGE production in the presence of free arachidonic acid. ○, Decidua (in 10 μM arachidonic acid); ●, decidua (under basal conditions); △, chorion (in 10 μM arachidonic acid); ▲, chorion (under basal conditions). For methods see text.

obtained at elective caesarean section. Other workers (Mitchell *et al.* 1978; Satoh *et al.* 1981) have found no differences in chorionic or decidual PG production *in vitro* in tissues obtained before or after the spontaneous onset of labour. Furthermore PG metabolism in the fetal membrane is similar before and after the onset of labour (Keirse *et al.* 1976).

Our data suggest that the net basal PGE production rate in chorionic and decidual cells is not affected by the mode of onset of labour and is similar in term and preterm labour. However, an important observation from this study is that the addition of arachidonic acid leads to a marked increase in PGE output in choriodecidual cells; thus, arachidonic acid availability seems to be the rate-limiting factor for PGE production. Okita *et al.* (1982) have demonstrated that arachidonic acid is liberated from tissue glycerophospholipids in amnion and chorion in early labour; hence, it is possible that the surge in intrauterine PG production associated with parturition (Keirse 1979; Turnbull 1983) is the result of increased availability of substrate, rather than increased activity of the PG synthetase system. Nevertheless, it must be pointed out that in the amnion PG synthetase activity seems to increase towards term (López Bernal *et al.* 1987).

The relation between steroid dehydrogenase activity and PG production is not clear. Both cortisol and progesterone have been shown to inhibit PG production in human endometrial cells *in vitro* (Skinner *et al* 1984; Kelly *et al.* 1985) and it has been suggested (Mitchell *et al.* 1982; López Bernal *et al.* 1982) that local progesterone and/or cortisol withdrawal in the fetal membranes-decidua area may contribute to increased PG production. However, tissue concentrations of progesterone and cortisol in amnion and choriodecidua remain stable before and after labour (López Bernal *et al.* 1982, Laatikainen *et al* 1982). Our findings indicate that HSD activity *per se* remains constant before and after labour and is not affected by spontaneous preterm labour. Nevertheless, both 3β- and 11β-HSD can be inhibited by a variety of steroids and the actual rate of pregnenolone to progesterone and cortisone to cortisol conversion *in vivo* would be determined by the availability of substrate from the maternal circulation and amniotic fluid and by the presence of inhibitors. Dehydroepiandrosterone and oestrone are strong inhibitors of choriodecidual 3β-HSD (Mitchell *et al.* 1982) and serial estimations of these two steroids in fetal blood and amniotic fluid in subhuman primates have demonstrated a significant increase in their levels before parturition (Walsh *et al.* 1984).

This study has shown no significant differences in steroid dehydrogenase activity between cells obtained after term and preterm labour. Attempts to predict preterm labour by steroid measurements in maternal plasma have been unsuccessful (Block *et al.* 1984), although recent data (Darne *et al.* 1986) suggest that preterm labour in the absence of premature rupture of the membranes is preceded by a prematurely elevated oestriol/progesterone ratio in maternal saliva Moreover, PGE production was similar in choriodecidual cells obtained after spontaneous term and preterm labour. This is in contrast to the PGE production rate in amniotic cells which is significantly lower after spontaneous preterm labour compared with spontaneous labour at term (López Bernal *et al.* 1987). Thus, in uncomplicated preterm labour, the steroid dehydrogenase activity and PGE output in choriodecidual cells are similar to that of cells obtained at term, but there is an elevated choriodecidual/amniotic PGE production ratio. Whether these changes in cell metabolism are causally related to the premature onset of labour remains to be elucidated. We are currently extending our studies to look at the possible effect of premature rupture of the membranes on prostaglandin production and steroid metabolism in amnion and choriodecidua.

In summary, decidual cells have a high capacity for cortisol and progesterone synthesis from their immediate precursors and have a relatively high PGE production rate; chorionic cells have a high 3β-HSD activity, but their net PGE output is low. These activities are well established from about 30 weeks gestation and do not change towards term or in relation to the mode of onset of labour. But the possibility remains that changes in the availability of endogenous substrates and/or inhibitors result in local changes in steroid or PGE output in relation to parturition *in vivo*.

Acknowledgment

This work was supported by Action Research, The National Fund for Research into Crippling Diseases.

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Received 30 October 1986
Accepted 3 March 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1059–1067

Rest versus heavy work during the last weeks of pregnancy: influence on fetal growth

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Summary. The influence of rest versus hard work on fetal growth at the end of pregnancy was assessed prospectively in a population of women who normally work hard during pregnancy. A group of 554 women living in Kalima area (Central Zaire) was admitted for rest in a maternity village for a median duration of 22 days. Self-selection, age, parity, number of living children, socio-economic status, maternal weight and height and gestational age were controlled for. Energy intake estimated in a sample of women in the maternity village and a sample of those staying at home was similar. Protein intake was found to be higher in the resting women. The duration of rest had a strong influence on birthweight and length in the newborn females but to a lesser extent in the newborn males. There was a 7·5-fold decrease in the rate of low birthweight in girls when the duration of maternal rest was >21 days. In boys the low-birthweight rate remained unchanged. Although this sex difference could not be explained it is concluded that, in developing countries, avoidance of heavy work can help to raise birthweight and perhaps reduce perinatal mortality.

Clinical experience and epidemiological data have suggested that heavy work exerted during the last trimester of pregnancy may be harmful to the fetus; it is thought that babies born to working mothers are smaller and have higher rates of perinatal mortality and preterm birth. These issues have been addressed in several retrospective studies (Peller 1917; Letourneur 1897; Balfour & Talpade 1930; Holemans 1960; Tafari *et al* 1980; Illsley *et al.* 1953; Stewart 1955; Naeye & Peters 1982; Mamelle & Laumon 1984) However, some studies lack standardization for socio-economic status or for parity (Stewart 1955; Letourneur 1897; Tafari *et al.* 1980), others do not control for self-selection bias (Peller 1917; Holemans 1960) and in all but two (Naeye & Peters 1982; Mamelle & Laumon 1984) gestational age was not assessed.

The absence of convincing clinical evidence probably explains why most authorities have not adopted specific strategies in this field. In developing countries, increased attention has been focused on nutritional intervention. The few maternity villages created in the 1950s

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(Stewart 1955), where women could rest at the end of pregnancy, have not met with success. There is indeed no recent report on such institutions.

Since 1953, in Kalima (Central Zaire), pregnant women from distant mining villages as well as pregnant wives of farmers living in traditional villages come and spend the last weeks of their pregnancy in a maternity village attached to the maternity hospital. This gave us the opportunity to conduct a prospective survey of the effects of rest versus heavy work on fetal growth during the last weeks of pregnancy.

Subjects and methods

Kalima is situated in the rain forest of East-central Zaire. The climate is hot and humid with little seasonal variation. The hospital of the Sominki mining company is served by a large network of health centres and dispensaries. This medical organization covers a community of 70 000 people. A third of them live in mining villages, another third live in traditional villages and the remaining third live in a semi-rural complex within 5 km of the hospital. Most of the people in the mining villages are of Bantu origin, the majority belonging to the Rega tribe. In the traditional villages, all are Rega. The estimated annual number of births in the area was 2700 of which 57% occurred in the maternity hospital. Almost all the wives of the mine workers were delivered in the maternity hospital. Delivery was free of charge for the women coming from traditional villages if they had attended antenatal clinics. Antenatal care consisted of monthly clinics during which the pregnant women were examined. Prophylaxis against malaria (50 mg pyrimethamine monthly) and supplements of iron and folic acid were also given.

Our aim was to study the effect of rest versus hard work during the last weeks of pregnancy in healthy women from a homogeneous socio-economic background. Therefore, we limited our study to liveborn singleton infants born at term (⩾38 weeks gestation) to healthy women of miners or peasants, parity 1–7 (including the index infant), who came from distant (minimum 6 km) mining and traditional villages where there was no possibility of medical assistance for delivery. We included women who stayed at least one day in the maternity village. Women with an obstetric history of more than one perinatal death, who were considered at higher obstetric risk, were excluded.

Out of a total of 3495 singleton live births between June 1980 and December 1982, 593 occurred in women who had not more than six children, lived outside Kalima and were admitted to the maternity village. Of these, 11 were excluded because of a history of more than one perinatal death, two were excluded because of preterm birth, 25 because fetal age was not determined and one because of significant maternal proteinuria Of the 554 women included in the study 458 were multiparous and 96 were primiparous, the two parity groups were analysed separately

Pattern of activity and dietary intake

To confirm the apparent difference in activity between home and maternity village, the pattern of activity was studied during January 1982 in a small random sample of 21 pregnant multiparae in their ninth month; six women in the maternity village and 15 in two mining villages Split-time analysis was used to study the activities inside the village and a detailed questionnaire was used for the activities outside the village. The following activities were defined as hard work: going to and returning from the field (during the return trip the women usually carried a basket with a load weighing between 20 and 40 kg), working in the field, and fetching water and wood. Domestic work was defined as light work (at home, the heavier activities were mainly done by a younger relative) Sitting or lying on a mat was defined as rest

During the same period, dietary consumption was determined during a 24-h period by weighing food products before and after meals in 20 and 18 pregnant women in their ninth month in the maternity village and in two rural villages respectively.

Surveillance of food intake outside the home was not done.

Stay in the maternity village

About 1 month before term, pregnant women were transported to the maternity village. The nurse's decision was based on the estimated date of delivery obtained from the antenatal file and also according to the timetable of the ambulance which visited the villages monthly.

The women leaving for the maternity village were generally accompanied by any of their children under 5 years of age and by a female relative. They took with them most of their food, the rest being brought at regular intervals by their family. The intervention in the maternity village was limited to lodging facilities, distribution of rice once a week and waterpipe distribution.

In multiparae, three subgroups were distinguished according to the number of days spent in the maternity village before delivery; a 'short stay' was defined as less than 7 days, a 'medium stay' was between 7 and 21 days and a 'long stay' was a stay lasting >21 days. Because the number of primiparae was too small they were divided into two groups only: a stay of ≤21 days and a stay of >21 days.

Maternal variables

Age, past obstetric and reproductive history, number of children still alive and socio-economic status were obtained at the first antenatal visit. Height was measured with a precision of 0·5 cm with a Stanley 'microtoise'. Weight was measured just before delivery. The duration of pregnancy at the start of antenatal care was calculated by subtracting the total number of weeks of antenatal care from the gestational age as assessed in the newborn.

Neonatal variables

Birthweight was measured with a precision of 10 g. Crown–heel length (measured to the nearest mm) and gestational age were assessed by the same trained nurse during the whole study period, except for one month, during which this was done by the first author (J.P.M.). The Lubchenco scheme adapted by Boersma & Mbise (1979) was used. The weight (W) for height (H) ratio was computed for each child using the Rohrer index (W/H^3).

Statistical methods

To standardize for gestational age, an individual standard deviation (SD) score was computed for birthweight and length, i.e. the weight or length value was subtracted from the mean value corresponding to the gestational age of the newborn under consideration and the result was divided by the corresponding SD. The SD score was calculated using the local intrauterine growth curves derived from male and female singletons born to women of the same social class living in the vicinity of the hospital who did not stay in the maternity village ($n = 1849$). The means (SEM) for all variables in the different duration-of-stay groups were tested by the contrast procedure (general linear model analysis) (Statistical Analysis System 1982) when three groups were compared and by the two-tailed Student's *t*-test when two groups were compared.

For the comparison of time devoted to rest and heavy work in the maternity village and in the villages, the one-tailed Mann–Whitney *U*-test was used.

Daily energy intakes were compared with Student's *t*-test. Daily intakes of protein were compared with the median test. The numbers of women coming from traditional and mining villages were compared with the χ^2-test.

Regression equations of SD score of birthweight on duration of stay in the maternity village for male and female infants (from the multiparae group) and the covariance of the two equations were computed. All statistics were calculated with the Statistical Analysis System implemented on an IBM 4300 computer.

Results

Proportions of daily hours spent at rest, light work and heavy work at home and in the maternity village are shown in Fig. 1. Women in the maternity village rested much more and spent less time doing heavy work than women in the villages. The differences were statistically highly

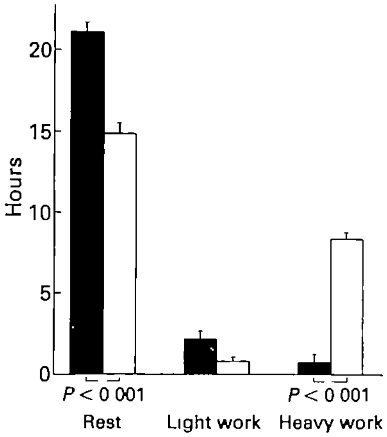

Fig. 1. Mean time (SEM) devoted to rest, light and heavy work during a 24-h period by six multiparae in the maternity village (■) and 15 multiparae in two mining villages (□) One-tailed Mann-Whitney *U*-test)

significant. The caloric intake did not differ significantly between the maternity village and the rural villages. Protein consumption was significantly higher in the maternity village group. Intake of palm oil (fat) was similar in the two groups and constituted about 40% of the total energy intake (Table 1).

Overall, the median duration of stay in the maternity village was 22 days (range 1–67 days). The characteristics of the multiparous women in the three different duration-of-stay groups are shown in Table 2. Maternal variables were similar in the three groups except for a slight but significant difference ($P<0{\cdot}05$) in the starting dates of antenatal care between the 1–7 days and the >21 days groups. The proportion of women coming from traditional villages was similar.

Table 1. Daily energy, protein and fat intake in the maternity village and two rural villages

Dietary intake	Maternity village (*n* = 20)	Rural villages (*n* = 18)
Energy (MJ)		
mean (SEM)	15·3 (0·9)	13·8 (1·1)
Protein (g)		
median (range)	44·4 (17·7–166·6)	24·3 (6–63·4)*
Palm oil (fat) (g)		
mean (SEM)	168·8 (24)	155·6 (21·8)

Significance of difference between the two groups *$P<0{\cdot}001$; median test

Table 2. Maternal characteristics of multiparae in the different duration-of-stay groups

Variable	Duration-of-stay groups 1–7 days (*n* = 71)	 8–21 days (*n* = 150)	 >21 days (*n* = 237)
Duration of stay (days)	4·1 (0·2)	14·2 (0·3)	36·6 (0·7)
Age (years)	24·9 (0·6)	24·9 (0·4)	25·0 (0·3)
Height (cm)	153·9 (0·7)	153·3 (0·5)	153·9 (0·4)
	(*n* = 53)	(*n* = 107)	(*n* = 181)
Weight (kg)	53·7 (0·8)	53·0 (0·5)	54·4 (0·5)
	(*n* = 69)	(*n* = 145)	(*n* = 234)
Gestation at start of antenatal care (weeks)	23·4 (0·9)	21·3 (0·6)	20·8 (0·5)
Proportion from traditional villages (%)	45·1	42·0	41·8
Parity*	4 (2–7)	4 (2–7)	4 (2–7)
No of living children*	2 (0–6)	2 (0–6)	2 (0–6)

* Values are medians (range) and include the index infant, other values are means (SEM) where appropriate

The gestation at start of antenatal care was significantly earlier in the >21 days duration-of-stay group $P<0{\cdot}05$ (contrast)

Gestational age at delivery was significantly lower for female infants in the short-stay group than in the medium- or long-stay groups. The difference was not significant for boys (Table 3).

Birthweight and length of the female newborns (crude data as well as data standardized for gestational age) were strongly influenced and increased as maternal rest was prolonged (Figs 2 & 3, Table 3). In male newborns the benefit associated with maternal rest was far less pronounced for birthweight and length (Table 3) and when these values were standardized for gestational age, the difference became not significant (Figs 2 & 3). In girls, the Rohrer index was not influenced by maternal rest (Table 3). This indicates that fetal growth was influenced in the same proportion for weight and for height and also suggests that the weight gain was not due to accumulation of fat. The rate of low birthweight decreased spectacularly with duration of rest in girls and remained unchanged in boys (Table 3). The regression of the SD score for weight on duration of stay in the maternity village was significant ($P<0{\cdot}0001$) only for the girls (Fig 4). Analysis of covariance of the two regression equations ($P<0{\cdot}0002$) confirmed that in our study the effect of rest on birthweight was obvious in girls and absent in boys.

The primiparae in the >21 days group were significantly younger ($P<0{\cdot}05$) than those in the ≤21 days group (Table 4). The SD score for birthweight in girls was significantly ($P<0{\cdot}05$) higher in the >21 days group (Fig. 5) whereas the SD score for body length did not reach significance (not shown) In boys, there was no difference between the two groups Gestational age for firstborn boys and girls was not significantly different between the two duration-of-stay groups (not shown).

Discussion

In the Kalima area, multiparous women who stayed 1 month in the maternity village showed a mean birthweight gain of 334 g and an increment

Table 3. Neonatal variables in the different duration-of-stay groups (multiparae)

Variable	Duration-of-stay groups 1–7 days	 8–21 days	 >21 days
	(*n* = 41)	(*n* = 79)	(*n* = 126)
Girls			
Birthweight (g)	2847 (48)	3109 (40)	3243 (36)
	└─**─	─┘└─*─	─┘
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Birth length (cm)	47·1 (0·30)	48·2 (0·17)	48·7 (0 14)
	└─**─	─┘ (*n* = 76) └─*─	─┘
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Rohrer Index (kg/m³)	27·3 (0·51)	27·7 (0·32)	27·8 (0·23)
Gestational age (weeks)	39·7 (0·19)	40·2 (0·13)	40·5 (0·10)
	└─*─	─┘	
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Low birthweight (%)	12·2	5·1	1·6
Boys	(*n* = 30)	(*n* = 71)	(*n* = 111)
Birthweight (g)	3104 (71)	3136 (44)	3271 (41)
		└─*─	─┘
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Birth length (cm)	48·2 (0 37)	48·4 (0·21)	49·0 (0·19)
		(*n* = 66)	(*n* = 110)
	└────	*	────┘
Rohrer Index (kg/m³)	27·7 (0·44)	27·3 (0·39)	27·7 (0·25)
		(*n* = 66)	(*n* = 110)
Gestational age (weeks)	40·0 (0·23)	40·1 (0·12)	40·4 (0·10)
Low birthweight (%)	3·3	4·2	2·7

Results are means (SEM) where appropriate.
n = number of subjects
Significance of difference between the groups (contrast test). * *P* < 0 05; ** *P*<0·001, *** *P*<0·0001

of 1·8 cm in mean length in female babies born at 40 weeks gestation. By studying the effect of duration of rest in the women who were admitted to the maternity village, the comparison of the different groups was not biased by self-selection. The population studied was limited to the pregnant wives of the miners and of the village farmers living outside Kalima. Women belonging to these two groups, whether pregnant or not, shared the same way of life characterized by a heavy workload throughout the year. However, their pattern of activity changed radically once they were admitted to the maternity village. We assumed that the difference in level of activity found between the small samples of the maternity village and the village women reflects the overall difference between the two groups. During a 24-h period, women in the maternity village spent 88% of their time lying on a mat or on a bed and only 3% at heavy work while those who remained at home spent 35% of their time at heavy work and 62% at rest. The different duration-of-stay groups in multiparae are otherwise similar for age, height, weight, parity, number of children still alive and proportion of women living in traditional villages.

The date of entry to the maternity village depended on the clinical assessment of the duration of pregnancy by the nurse at the beginning of antenatal care and was thus not influenced by the woman's condition at the time of referral to the maternity village.

There is no reason to suspect a systematic bias in the estimation of gestational age of the newborn babies and their allocation to the different gestational age classes up to 42 weeks. However, the inclusion of babies born after ≥43 weeks gestation in the 42-weeks class probably resulted in a downwards shift of the mean start of antenatal care (derived from date of start, date of birth and gestational age).

In a small sample of women, energy intake was found to be similar before and after admission to the maternity village. It amply met the requirements of a working pregnant woman (WHO 1974; Durnin *et al.* 1985). Before and after admission to the maternity village, 40% of the energy intake was composed of fat in the form of palm oil. This high proportion is due to the use of palm oil to make boiled green leaves more palatable.

The higher proportion of protein consumed in the maternity village can be attributed to the women coming from the bush, using the opportunity to buy meat, fish and other extras.

A 24-h survey does not allow an accurate estimate of the intake of animal protein. Food of

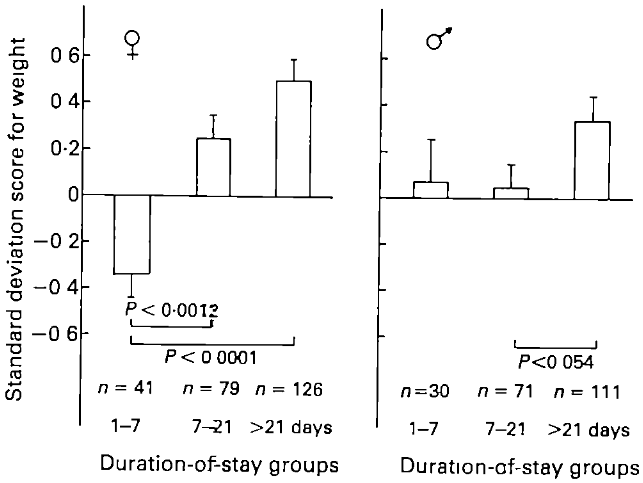

Fig. 2. Mean standard deviation score (SEM) for birthweight by duration of stay in multiparae

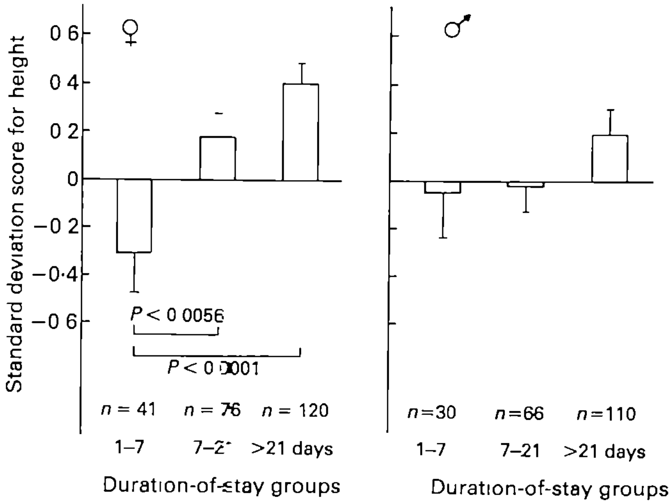

Fig. 3. Mean standard deviation score (SEM) for birth height by duration of stay in multiparae.

animal origin is a luxury food consumed very irregularly and the results would have been more correct if the study had covered a 1-month period. But it is possible that the higher protein intake in the maternity village was a factor favouring fetal growth.

Since energy intake was similar and energy output high in the home village, women in the maternity village had a more favourable energy balance. However, except in situations such as wartime (Smith 1947) or very restricted diet (Grieve *et al.* 1979), a positive influence of nutritional supplementation on birthweight remains controversial and, when present, is limited to male newborns (Mora *et al.* 1979; Rush *et al.* 1980, Lechtig *et al.* 1975; McDonald *et al.* 1981; Adair & Pollitt 1985).

In Gambia, Prentice *et al.* (1983) found that overall mean birthweight increased by 224 g when nutritional supplementation was given to pregnant women during the rainy season. Women were normally in negative energy balance during the rainy season due to food shortage and heavy agricultural work.

However, in all these situations, nutritional supplementation was provided to women having a marginal nutritional intake. In contrast, the women we studied had an abundant energy

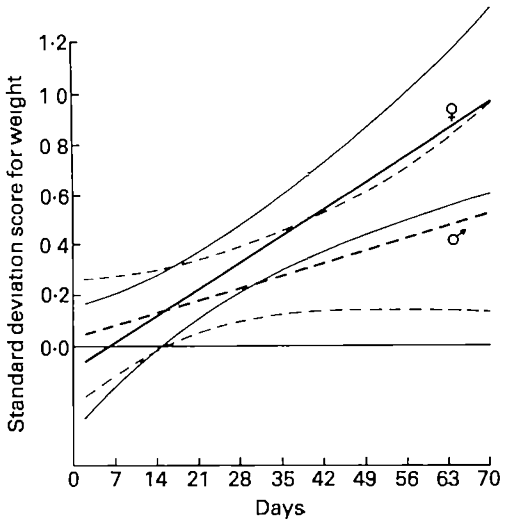

Fig. 4. Regression of standard deviation score for birthweight on duration of maternal stay in male and female infants The 95% confidence limits are also shown (multiparae).
♀ ═══, r = 0·24, ♂ ╌╌╌, r = 0·11.

intake. We believe that the major part of the observed effect can be ascribed to avoidance of heavy work which has been shown to diminish the uteroplacental perfusion (Morris *et al.* 1956). During heavy work, the blood volume available to the fetus is reduced and consequently so are the amounts of nutrients and oxygen (Widdowson *et al.* 1980).

Furthermore, Artal *et al.* (1984) have shown that sustained strenuous exercise raises the catecholamine levels and results in bradycardia probably due to fetal hypoxaemia. The loss of water and electrolytes associated with hard work in a hot climate, and the resultant reduction in plasma volume, might also play a deleterious role (Hytten 1984).

Whether the position, recumbent versus upright, also played a role needs to be considered. Indeed, Balfour (1938) and Naeye & Peters (1982) have observed a difference in birthweight between sitting and standing workers. This topic has been reviewed extensively (Briend 1980). Our data do not allow us to distinguish between the effects of rest and of position

In primiparae, the mean SD score for birthweight was significantly greater only in the female infants born in the long-stay group. This less clearcut effect may result from the traditional attitude of the community towards the first pregnancy; most women who are pregnant for the first time are pampered and frequently return to their parents' home until delivery. Furthermore, age less than 15 years was a risk factor for which special care was considered and referral to the maternity village was planned earlier. This explains why the primiparous women in the long-stay group had a lower mean age and height and also started antenatal care earlier; despite being younger and shorter, those who gave birth to a girl still benefitted from rest in the maternity village. In both parity groups only female infants benefitted from maternal rest. This sex difference is the reverse of findings from nutritional supplementation studies where newborn male infants were found to benefit more than the female infants (Mora *et al.* 1979; McDonald *et al.* 1981). While we cannot offer an explanation for this unexpected sex difference, we feel that these results suggest that rest and nutritional supplementation have a different mode of action.

In a study on twin pregnancy, Saunders *et al.* (1985) reported that although hospital rest reduced the rate of low birthweight, it had a negative effect on the length of gestation. Length of gestation is negatively influenced by hard physical activity (Balfour 1938; Stewart 1955; Mamelle & Laumon 1984) and it is essential to control for this variable. In our study, the time of referral to the maternity village pre-

Table 4. Maternal characteristics of the primigravidae in the two duration-of-stay groups

Variable	Duration-of-stay groups ≤21 days (n = 47)	 >21 days (n = 49)
Duration of stay (days)	11·0 (0·9)	37·0 (1·5)
Age (years)	17·6 (0·5)	16·3 (0·2)*
Height (cm)	153 1 (0·9) (n = 35)	150 8 (1 0) (n = 34)
Weight (kg)	51·3 (0·9) (n = 46)	50 7 (0·8) (n = 47)
Gestation at start of antenatal care (weeks)	22·4 (1·1)	21·0 (1·0)
Proportion coming from traditional villages (%)	68 1	69·4

Results are means (SEM)
Significance of difference between the two groups
* P<0·05

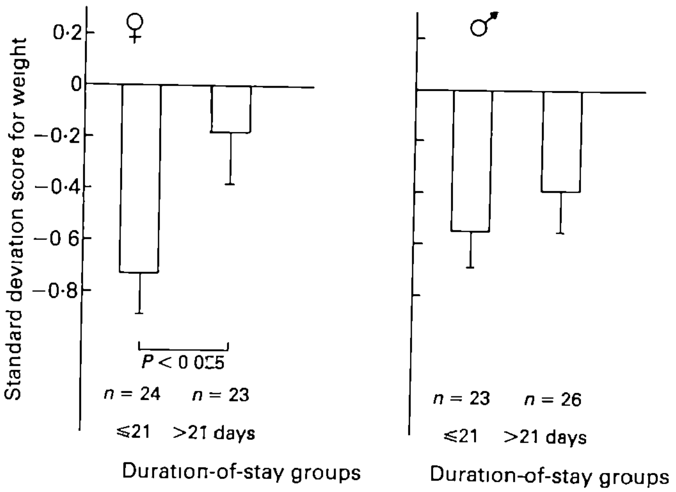

Fig. 5. Mean standard deviation score (SEM) for birthweight by duration of stay in primiparae

cluded analysis of the effect of heavy work on the rate of preterm delivery.

It is not surprising that avoidance of heavy work at the end of pregnancy benefits fetal growth, but the size of the effect, particularly with regard to the duration of the intervention, is striking. This also raises the question whether, in studies of nutritional supplementation in pregnancy, a possible positive effect could have been partly masked by the increased activity of the pregnant women (Adair & Pollitt 1985). We conclude that, in the situation of the women studied, staying in a maternity village during the last weeks of pregnancy is a cost-effective programme to increase birthweight. As an added advantage, we can expect that neonatal morbidity and mortality related to amniotic infection caused by sexual intercourse in late pregnancy (Naeye 1980) would be reduced.

Some of the above issues could be clarified by further research such as a trial of pregnant women randomly allocated to home or maternity village for varying lengths of time.

Acknowledgments

We are particularly grateful to Professor I. MacGillivray for his stimulating criticisms and suggestions, to Reverend Sister Bertha from the Kalima maternity hospital for her unfailing help and to our colleagues from the Study group for Maternal and Child Health in the Tropics, Professor J. Vuylsteke, Dr H van Loon, Dr M. Tshibemba and Mrs de Hemptinne.

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Received 18 December 1985
Resubmitted 25 November 1986
Accepted 3 February 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1068–1073

In-utero intravascular transfusion of the fetus for the management of severe Rhesus isoimmunization—a reappraisal

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Summary. Ten fetuses, severely affected by Rhesus (D) haemolytic disease, received one to three intravascular blood transfusions at between 18 and 30 weeks gestation, with the use of fetoscopically guided needles into one of the umbilical cord vessels. Although the technique was successfully accomplished in all cases, the fetal response to the procedure was varied. Only two fetuses survived beyond the neonatal period, and one child subsequently died principally because of the problems resulting from premature delivery. The reason for the low rate of survival has been explored and the continued use of the method described is now questioned.

In severe cases of erythroblastosis fetalis due to Rhesus (D) incompatibility occurring during the first 24 weeks gestation, intraperitoneal transfusion of the fetus has generally been unsuccessful (Holt *et al.* 1973; Frigoletto 1974, Bock 1976). In an attempt to improve the prospects for such pregnancies, the concept of intrauterine intravascular transfusion of the fetus was introduced (Rodeck *et al.* 1981; MacKenzie *et al.* 1982, Bang *et al.* 1982). It was postulated also that this approach combined with fetal blood sampling might allow a more precise management of sensitized pregnancies.

Patients and methods

The decision to advise intravascular transfusion of the fetus was made after observing trends in maternal antibody concentration, amniotic fluid ΔOD^{453} values and fetal haematocrit. Transfusions were performed fetoscopically as described previously (MacKenzie *et al.* 1982) after premedication with morphine 10 mg and scopolamine 0·2 mg given intramuscularly 1–2 h before operation, and diazepam 5 mg given intravenously immediately before the procedure; site of entry into the amniotic sac was determined by ultrasound at which point a solution of xylocaine with adrenalin was injected down to the myometrium. In each case an umbilical cord vessel was used for the transfusion procedure and a suitable position was selected, generally near the insertion of the cord into the chorionic plate, where mobility of the cord was reduced. In all instances dry syringes and needles were used without prior priming with anticoagulant.

The technique developed initially was similar to that originally used for exchange transfusion in newborn infants (MacKenzie *et al.* 1982). An umbilical artery was preferred for the transfu-

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sion although occasionally the vein was also used. Between 2 and 5 ml fetal blood was aspirated depending on the gestational age and the haematocrit was checked immediately. In the earlier patients a transfusion was given if the haematocrit was <35% up to 25 weeks gestation, and <40% at later gestations. Subsequent experience, however, encouraged us to modify these figures to <30% for all fetuses. Donor blood of group O Rhesus negative and CMV-antibody negative was drawn using CPD-A1 as anticoagulant. This blood was packed to a haematocrit of 60–75%, crossmatched against maternal serum and used within 24 h of collection; it was buffered with THAM solution to a final pH of 7·20–7·35 immediately before transfusion. Except for the first five patients, blood was always irradiated before use.

For every 5 ml fetal blood removed, 10 ml donor blood was transfused, initially at a rate of 1–2 ml/min and subsequently at 0·5–1·0 ml/min. The transfusion was continued until the fetal haematocrit reached approximately 40% as demonstrated by testing aliquots of blood removed from the fetal circulation during the transfusion. With the exception of the first two cases, continuous fetal heart activity was observed with real time ultrasound throughout the procedure; the transfusion was interrupted if an arrythmia developed, and only restarted when the sinus rhythm was re-established. Cardiac stimulants and diuretics were not given. After transfusion, cardiac activity was continuously monitored for the first few minutes, and if it was satisfactory it was only rechecked at intervals before discharge the next day; if the fetal heart rate pattern was unsatisfactory, cardiotocography was continued for a longer period Repeat transfusions were planned empirically at 2–3 week intervals with a view to reaching 30 weeks gestation before considering delivery, with due weight given to the amniotic fluid phosphatidyl glycerol concentration. As a result of technical difficulties in the first patients, the volume of blood removed from the feto-placental circulation was reduced, and a maximum of 5 ml blood was withdrawn for each 20 ml transfused.

Results

The ten fetuses received a total of 17 transfusions (Table 1). Although nine fetuses survived the first transfusion, in two instances the procedure was abandoned because of a fetal bradycardia. Only two of the six fetuses transfused twice survived beyond 24 h. The fetus transfused three times died within 6 h of the third procedure. Only two fetuses survived the neonatal period

One of the two fetuses (no. 8) with a marked bradycardia during the first transfusion was given 8 ml of blood at 28 weeks gestation; because the bradycardia persisted at 50 beats/min, caesarean section was performed immediately. The infant weighed 920 g and was found to have a metabolic acidosis at birth, in addition to the stigmata of severe erythroblastosis fetalis. Three neonatal exchange transfusions were performed but the baby subsequently suffered a large intraventricular haemorrhage and died at 9 months of age. The other fetus (no 7) developed a bradycardia during the first transfusion at 25 weeks and did so after receiving less than 3 ml of blood; the bradycardia persisted for 4 min and the procedure was abandoned. An ultrasound scan had shown this fetus to be very hydropic with a cardiac arrythmia. Following unsuccessful intraperitoneal transfusion, a second attempt at intravascular transfusion was made at parental insistence 9 days after the first had been abandoned. The degree of hydrops was then greater and the frequency of bradycardia increased During the transfusion cardiac embarrassment worsened, such that the procedure was terminated after 30 ml of blood had been given. At this stage the heart appeared to be in tamponade; asystole was finally noted approximately 2 h later.

In four other patients there was a similar chain of events: bradycardias occurred in patients nos 3, 4, and 10 during the second transfusion and in no. 5 during the third transfusion; this last fetus was the only one of the six who developed a bradycardia who was not hydropic when born within 36 h of intrauterine death.

The three other fetal losses (nos 1, 6 and 9) were associated, respectively, with severe anaemia, coincidental placental failure due to a large pre-existing placental infarct and spontaneous abortion 4 days after transfusion. In the patient with placental infarct, the fetal blood gas values in the umbilical artery blood collected at the start of the transfusion were acidotic compared with the values obtained in this department in samples from unstressed, non-isoimmunized fetuses (MacKenzie *et al.* 1986).

The only pregnancy (no. 2) with a successful outcome involved the most mature fetus in the

Table 1. Characteristics and outcome for 10 fetuses after in-utero intravascular transfusions

Patient no	Gestation at transfusion (weeks)	Maternal anti-D (i.u./ml)	ΔOD^{450}	Haemoglobin (g/dl)		Kleihauer (%) fetal		Volume transfused (ml)	Hydrops	Outcome
				Before	After	Before	After			
1	18	594	NR	2·4	11·1	100	20	15	No	IUD during transfusion
2	28	80	0·295	11·3	14·0	100	30	67	No	Uncomplicated transfusion
	30	88	0·240	7·2	14·0	55	10	97	No	Born at 32 weeks, Hb 12 g/dl
3	25	50	0·660	3·0	15·0	100	30	50	Yes	Uncomplicated transfusion
	27	96	NR	4·0	15·9	1	1	70	Yes	IUD at 12 h, hydropic
4	19	28*	0·180	9·1	11·7	100	NR	10	No	Uncomplicated transfusion
	21	34	NR	6·3	12·0	95	50	20	Yes	IUD during transfusion, hydropic
5	20	40	0·140	8·9	11·0	100	40	20	No	Uncomplicated transfusion
	23	40	0·310	6·9	13·1	90	20	40	No	Uncomplicated transfusion
	25	25	NR	9·2	11·3	40	10	30	No	IUD 90 min after transfusion
6	27	60	0·150	12·1	NR	100	50	35	No	IUD 12 h after transfusion, placental infarct, non-hydropic
7	24	750	0·605	8·3		100		3	Yes	Transfusion abandoned because of bradycardia
	25	643	NR	6·0	16·0	100	NR	30	Yes	IUD 2 h after transfusion, hydropic
8	28	13*	0·473	8·3		100	NR	8	Yes	Bradycardia with transfusion, immediate LSCS (see text), Hb 7·8 g/dl, hydropic
9	19	195	NR	2·0	12·3	100	10	17·4	No	Miscarriage after 5 days
10	23	70	0·650	3·3	14·0	100	5	60	Yes	Uncomplicated transfusion
	25	52	NR	5·5	12·3	NR	1	30	Yes	IUD 2 h after transfusion, hydropic

* Undergoing plasmapheresis

NR, Not recorded, IUD, intrauterine death, LSCS, lower segment caesarean section.

study; two transfusions were given at 28 and 30 weeks gestation. In the absence of signs of acute cardiac strain, this fetus was given larger volumes of blood than any other in this group. This non-hydropic fetus, born at 32 weeks, received four exchange and one top-up transfusion during the neonatal period, and has since progressed well.

Discussion

Although 15 years have passed since the introduction of prophylaxis, maternal anti-Rh (D) sensitization is still widely encountered and its prevalence (2·6 per 1000 births) has changed little during the last decade. Although improved obstetric and paediatric management has done much to reduce the number of perinatal losses, the overall fetal loss rate of 0·12 per 1000 births (Bowell *et al.* 1985) is still unacceptably high Because many of the fetal losses now occur during the second trimester it was hoped that direct intravascular transfusion using a fetoscope would serve to reduce fetal wastage. Although our initial work and the reports of others (Rodeck *et al.* 1984; de Crespigny *et al.* 1985) offered considerable hope, the results reported here are disappointing, and a number of possible explanations have been considered.

The three fetal losses after a first transfusion are readily explained: spontaneous abortion; aspiration of too much blood from the fetal circulation resulting in acute cardiac failure in the severely anaemic fetus at 18 weeks gestation; and a pre-existing placental infarct leading to hypoxaemia exacerbated by the transfusion. At the time of transfusion the significance of the abnormal fetal blood gas values was not appreciated. Four of the six fetuses undergoing a second transfusion died within 24 h of the procedure; all were hydropic when stillborn 24–36 h later One of the two that survived the second transfusion died shortly after a third transfusion but was not hydropic; the other was born 2 weeks later in good condition. All five fetuses that died had bradycardias leading to poor cardiac filling both during and immediately after the transfusions. Postmortem histological examinations (to be reported elsewhere) revealed myocardial infarctions suggesting acute cardiac strain consequent upon the transfusion, but probably secondary to the effect of severe haemolysis.

It was initially postulated that exchange rather than direct transfusions might be preferable in order to reduce the risk of cardiac decompensation in the fetus already in incipient failure from the haemolytic process. Following the early poor fetal survival rate, however, the principle of exchange transfusion was abandoned and direct transfusion (Bang *et al.* 1982; Rodeck *et al.* 1984) was adopted, but the fetal survival was not improved.

The possibility of the transfusion rate being too rapid (1–2 ml over 2–3 min) was also considered. Restricting the flow rate, however, made no apparent difference to fetal response and two fetuses showed acute adverse reactions after the transfusion of less than 10 ml of blood at 0·5–1·0 ml/min. Furthermore, the transfusion rate used was lower than that reported by Rodeck *et al.* (1984) who had a successful outcome in 72% of transfused pregnancies

An attempt to assess cardiac function was made by measuring intravascular pressure in the umbilical vein and artery, and observing the effect on the fetoplacental circulation of transfusing or removing aliquots of blood (Castle & MacKenzie 1986), but no significant effect was observed. Cardiac overload seems even less likely since two fetuses developed irreversible failure after the transfusion of less than 10 ml.

The acute response could be due to vascular spasm at the site of transfusion, but vasospasm is generally visible through the fetoscope when it occurs at the time of blood aspiration; there was also no obvious blanching of the cord to indicate that this was happening although the possibility remains. The better results reported by de Crespigny *et al.* (1985) could, however, be due to transfusing into the umbilical cord vessels within the fetus where spasm may be less of a problem. We did not observe any difference in fetal response between the use of an umbilical artery or vein for the transfusion. Extravasation of transfused blood into Wharton's jelly causing extravascular compression and restricting the umbilical circulation was also considered, but postmortem studies of the cord failed to support this possibility.

The more delayed response, with fetal death during the 24–36 h after transfusion, suggests either increasing haemolysis or a possible toxic effect. Haemolysis of the transfused concentrated red cells was considered (MacDonald & Berg 1959; Wilcox *et al.* 1981; Mollison 1983) but our in-vitro studies that assayed both free haemoglobin and haptoglobin levels in donor plasma after the manipulation of blood under similar conditions through the transfusion needle did not show any recognizable haemolysis (P. J. Bowell *et al.*, unpublished observations). It is possible, however, that a more sensitive study of red cell survival, using radiolabelled cells, could demonstrate in-vivo haemolysis. A recently considered hazard of transfusion is the possible cardiotoxic effect of citrate anticoagulant of donor blood. If such a hazard exists this could compound the effect of possible potassium release from transfused blood (Batton *et al.* 1983). Wiley & Koepke (1985), however, did not find a detrimental effect in the infant due to potassium toxicity coupled with citrate, but the total volume transfused to the full term infants in their study was relatively small, ranging from 6 to 21 ml. Since adenosine or its metabolites might be responsible for the arrythmias seen before transfusion in the compromised fetus (Watt 1985), the situation could possibly be exacerbated or provoked by the transfusion of CPD-A1 blood (Finch 1985) although this seems unlikely given the small quantity of adenosine remaining in the plasma transfused.

Changes in fetal oxygenation with transfusion have been reported in sheep (Itskovitz *et al.* 1984). With one exception there was no indication that fetal oxygenation in severe Rhesus (D) haemolytic disease is compromised, except probably at the terminal stages, unless other problems coexist. Itskovitz *et al.* (1984) showed that blood containing HbA, which is used for transfusion, lowers the oxygen affinity and results in lower oxygen availability to fetal organs, thus altering blood flow which might decompensate the already compromised fetal heart

An acute graft-versus-host reaction could explain the acute responses in the majority of the repeat transfusions. Brubaker (1983) suggested that post-transfusion graft-versus-host disease with a short duration of 2–30 days may often go undiagnosed. Therefore, because there are reported cases following intrauterine transfusion (Chudwin *et al.* 1982) it was decided that all donor blood should be irradiated prior to transfusion; fetal losses nevertheless continued.

The possibility remains that many of the fetuses treated were already moribund at the time of transfusion, and that treatment may indeed have hastened fetal death. We have therefore re-examined our criteria for initiating intrauterine transfusion. Maternal anti-D potency, although capable of defining safe levels of antibody, does not allow accurate prediction of the outcome of severely affected pregnancies (Bowell *et al.* 1982). Although others (C. H. Rodeck, personal communication) have used an anti-D level of >4 i.u./ml before the 26th week of pregnancy as a threshold, with 85% successful outcome, we have found that 24/41 (60%) pregnancies with similar levels were successfully managed without intrauterine transfusion With one exception, the antenatal anti-D levels in our patients were >20 i.u./ml. Five other cases with levels greater than 20 i.u /ml, were referred to other units for intrauterine transfusion (both intraperitoneal and intravascular) and all, save one, resulted in intrauterine death. Amniotic fluid ΔOD^{453} values do not always correlate with the severity of the disease, probably because the fetal response to the haemolytic onslaught is variable. Indeed, one of the most valuable aspects of this study has been the demonstration of the importance of fetal haematocrit as the main indicator of erythropoietic compensation. Without the availability of this measure it is probable that many intrauterine transfusions, with all the risks outlined above, might be initiated prematurely.

Our results have clearly been most disappointing. Although technically every transfusion was successfully initiated, we are unable to explain fully the causes of our fetal losses We have reluctantly, therefore, had to reconsider the concept of fetoscopy, assisted intrauterine intravascular transfusion of the fetus severely affected by Rhesus (D) haemolytic disease. Preliminary findings, however, from a smaller number of cases using ultrasound guided needles for direct transfusion of the fetus, suggest that this method might be more successful. These data will be reported elsewhere when the study group size has grown and conclusions can be drawn.

Acknowledgments

We acknowledge with gratitude the assistance given by many colleagues at the John Radcliffe Hospital, and in particular Dr F. G. Bolton and Miss M. N. Jones, Department of Haematology, and Dr J. Keeling, paediatric pathologist.

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Received 30 October 1986
Accepted 20 March 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1074–1077

Doppler ultrasound assessment of fetal and uteroplacental circulations in severe second trimester oligohydramnios

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Summary. Doppler blood flow studies in 41 pregnancies with oligohydramnios in the second trimester found abnormal patterns in all 14 pregnancies with intrauterine growth retardation but in only one of nine pregnancies with premature rupture of the membranes, and one of 10 with fetal renal defects. Mixed patterns were found in a heterogeneous group of fetuses with other malformations or intrauterine infection. Unlike previous reports a diagnosis was achieved in all pregnancies, suggesting that Doppler studies should be an integral part of the antenatal investigation in such pregnancies.

Oligohydramnios in the second trimester is associated with premature rupture of the membranes, urinary tract and other fetal malformations, and intrauterine growth retardation. The differential diagnosis is often made difficult by poor ultrasound demonstration of fetal structures, due to loss of the acoustic window that the amniotic fluid provides. Further difficulties arise in the examination of macerated stillbirths when post-mortem findings are uninformative so that frequently the cause of the oligohydramnios remains unexplained.

The application of the Doppler principle to ultrasound has led to the development of a non-invasive means of assessing the fetal and uteroplacental circulations and there have been many reports demonstrating significant associations between Doppler waveform analysis and clinical outcome (Jouppila & Kirkinen 1986; Trudinger *et al.* 1985; Hackett *et al.* 1987). We have employed Doppler blood flow studies in the assessment of second trimester oligohydramnios, to determine what advantage such studies might contribute to the management of these cases.

Patients and methods

The study included 41 pregnancies, complicated by oligohydramnios before 26 weeks gestation, which were referred to our unit, from several centres, for a high resolution ultrasound examination and further investigation. Severe oligohydramnios was defined as the absence of any pockets of amniotic fluid with a vertical height >1 cm (Manning *et al.* 1981). The gestational age was calculated from an ultrasound scan at between 16 and 18 weeks gestation at either the referring centre or our unit. Fetal obstructive uropathies were excluded as the typical ultrasound features were apparent at the initial examination and the diagnosis made on this basis. Doppler blood flow studies of the fetal and uteroplacental circulations were performed at the first visit and these findings will be presented in this report.

We used a pulsed Doppler duplex apparatus with an on-line spectrum analyser (Kranzbuehler ADR 5000), with concurrent real-time imaging the Doppler sampling gate may be placed over the vessel of choice. Flow velocity

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waveforms (FVW) were recorded from the fetal aorta (Griffin *et al.* 1984) where there is normally continuous forward flow detectable above the 150 Hz filter. Absence of end-diastolic frequencies is indicative of pathologically increased peripheral resistance (Hackett *et al.* 1987) and this phenomenon was taken to indicate an abnormal fetal circulation. The FVW was also recorded from both left and right lateral uterine walls to assess the uteroplacental circulation (Campbell *et al.* 1983). An abnormal FVW was defined by a resistance index (Pourcelot 1974) of over 0·58 on either side, this value being 2 SD above the mean in the normal population.

The fetuses were divided into four groups according to the postnatal or postmortem findings, including all abortions and perinatal deaths. A karyotype was not available in all cases and thus it is possible that some chromosomal abnormalities may have been missed.

Group 1. This group included five fetuses with renal agenesis and five with renal dysplasia (Potter Type I in one and Potter Type II B in the other four).

Group 2. This group included eight fetuses with chromosomal anomalies, intrauterine viral infection, and dysmorphic syndromes not attributable to the presence of oligohydramnios alone. There were two with documented chromosomal defects, one with Turner's syndrome (45XO) and one with a triploidy (69XXX). In five fetuses multiple congenital anomalies were found involving cardiac, skeletal, and urogenital structures. In one infant hepatitis and cirrhosis resulted in early neonatal death and there was histological evidence of a viral embryopathy although the virus itself was not characterized.

Group 3. This group included 14 morphologically and chromosomally normal fetuses with idiopathic intrauterine growth retardation (IUGR). Ultrasound-derived abdominal circumference measurements and actual birthweights were below the 5th centile in 12 and on the 5th centile in the other two. For abortuses, a normal range of birthweight for gestational age constructed in this hospital was applied (Tsannatos, unpublished observations). When the gestational age was between 28 and 32 weeks, the birthweight charts of Gruenwald (1966) were applied, and thereafter the parity and sex specific charts of Thomson *et al.* (1968).

Group 4. This group included nine pregnancies with premature rupture of the membranes (PROM), the fetus having normal growth, morphology, and chromosome complement. A history of PROM was reported on referral in only one patient, the other eight admitted a history of PROM only on questioning following completion of our investigations.

Results

There were no consistent patterns of maternal age, parity, past obstetric history, or family history to aid assessment of the index pregnancy. The mean gestational age at presentation was 22·5 weeks (range 18–26) and there was no significant difference between the four groups.

The uteroplacental and fetal Doppler FVW findings and the outcomes are shown in Table 1. In total 22 (54%) pregnancies had abnormal FVW in the fetal, the uteroplacental, or in both circulations. Fetal abnormalities were found in 18 of the 41 pregnancies (44%) and only 5 (12%) infants survived.

Group 1. An abnormal blood flow pattern was seen in only one of the 10 fetuses in this group;

Table 1. Doppler findings and outcome in 41 pregnancies with second trimester oligohydramnios

		Flow velocity waveform								
		Normal	Abnormal				Outcome			
Group	*n*	*n* (%)	*n* (%)	Fetal	UPL	Both	TOP	IUD	NND	Alive
1	10	9 (90)	1 (10)	0	0	1	6	1	3	—
2	8	2 (25)	6 (75)	3	1	2	6	—	2	—
3	14	0 (—)	14 (100)	2	0	12	0	12	—	2
4	9	8 (89)	1 (11)	0	1	0	1	2	3	3

UPL, Uteroplacental circulation; TOP, induced abortion; IUD, intrauterine death or miscarriage, NND, neonatal death; Alive, surviving into early infancy.

none was growth retarded. The outcome for these fetuses was invariably fatal, primarily as a result of prenatal diagnosis and elective abortion.

Group 2. The two fetuses with chromosomal defects had abnormal fetal and uteroplacental FVW and both had an ultrasound abdominal circumference (AC) and actual birthweight below the 5th centile. None of the other fetuses in this group showed evidence of growth retardation, but in one fetus with an abnormal uteroplacental FVW alone, a dysmorphic syndrome was diagnosed

Group 3. All 12 fetuses with a birthweight below the 5th centile had both abnormal fetal and uteroplacental FVW; 10 of them died *in utero* and two survived. The other two fetuses in this group had birthweights on the 5th centile, they had normal uteroplacental but abnormal fetal FVW; both died *in utero.*

Group 4. All nine pregnancies with PROM had normal fetal FVW and in all but one the uteroplacental FVW was also normal. One of these nine pregnancies was electively aborted but three of the remaining eight resulted in surviving infants.

Discussion

Severe oligohydramnios in the second trimester of pregnancy has long been associated with a poor perinatal outcome (Koontz *et al.* 1983; Seller & Child 1980). Indeed, Barss *et al.* (1984) proposed that a pessimistic prognosis be given for the pregnancy 'regardless of the cause' of the oligohydramnios. However, Mercer & Brown (1986) reported a fetal survival rate of 18% in a series of 34 pregnancies. Most notable in previous reports has been the large proportion of women who elected to have the pregnancy terminated and the substantial number of cases in which the underlying pathology was not elucidated. The nature and natural history of a number of disorders leading to this condition therefore remain elusive. Clearly, there is a need to improve our diagnostic approach to this problem and so achieve a more rational basis on which to counsel women on the prognosis for both the current and future pregnancies.

The recent application of Doppler ultrasound technology to the assessment of the fetal and uteroplacental circulations has provided new insights into the pathophysiology of pregnancy. A highly pulsatile uteroplacental FVW, indicative of a high resistance placental bed, may be identified as early as between 16 and 20 weeks gestation when it was found in 10–15% of the population (Campbell *et al.* 1986). Whereas in some pregnancies this pattern has become normal by 24 weeks, in others it persists and is then associated with growth retardation and pregnancy hypertension (Campbell *et al.* 1983).

These findings are in keeping with previous observations of reduced uteroplacental blood flow (Browne & Veall 1953; Kaar *et al.* 1980) and restricted trophoblast invasion (Sheppard & Bonnar 1981) in these pregnancy complications. The presence of a fetal abnormality (with a normal karyotype) or of PROM does not preclude the presence of defective trophoblast and thus we would expect to see cases with an abnormal uteroplacental FVW irrespective of the fetal pathology. Thus, in groups 1 and 2 there are mixed fetal and uteroplacental patterns as might befit the varied pathologies within these groups. It appears that normal patterns tend to be seen with renal abnormalities. Two subjects in group 2, however, merit a special note in that it has been previously postulated that the presence of karyotypic abnormalities might result in defective trophoblast tissue (Battaglia 1978) and this would then be consistent with the mechanisms underlying reduced uteroplacental perfusion. Similarly Trudinger & Cook (1985) reported abnormal fetal FVW in all five chromosomally abnormal fetuses; although uteroplacental FVW was recorded in only one of them, this was normal.

The finding of an abnormal FVW in the uteroplacental circulation in 12 of the 14 pregnancies in group 3 provides direct evidence of an association between abnormal uteroplacental perfusion and second trimester pregnancy loss. Furthermore the presence of abnormal fetal FVW in this group suggests a mechanism for the associated oligohydramnios. Abnormal fetal FVW in fetuses with IUGR indicates a redistribution in the fetal circulation (Hackett *et al.* 1987) which may lead to reduced renal perfusion, oliguria, and thus the development of oligohydramnios. Of the two pregnancies in group 3 associated with an abnormal fetal FVW and a normal uteroplacental FVW, one was similar to the others in the group but the second pregnancy was complicated by a partial mole where, with a defective villous circulation, one might expect growth retardation and a high resistance pattern in the fetal circulation independent of the uteroplacental profile.

Finally, those pregnancies complicated by PROM have normal Doppler patterns, the one exception being consistent with the population incidence of abnormal uteroplacental patterns.

The findings in this retrospective study suggest that assessment of the fetal and uteroplacental circulations may be a useful adjunct to the investigation of pregnancies complicated by oligohydramnios in the second trimester. Normal uteroplacental and fetal waveforms should alert the ultrasonographer to the presence of a renal abnormality or of PROM. The patient should be questioned further about ruptured membranes and if this proves negative, adjuvant techniques, such as the intra-amniotic instillation of saline, may be used to enhance the imaging of fetal anatomy. Neither the maternal (Harman 1984), nor the direct fetal (K. H. Nicolaides, in preparation), administration of diuretics is reliable in distinguishing the renal from the non-renal causes of oligohydramnios. Abnormal fetal and uteroplacental flow patterns associated with fetal measurements below the 5th centile indicate IUGR and fetal karyotyping would then be advised (Nicolaides *et al.* 1986).

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Received 2 October 1986
Accepted 19 March 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp 1078–1083

Reproductive performance following conservative microsurgical management of tubal pregnancy

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Summary. Between 1981 and 1986, 58 women underwent conservative surgery for ectopic pregnancy; 30 had both tubes present, and 28 had the operation on their single tube. Twenty-five of the 30 women with both tubes present desired pregnancy; 17 (68%) conceived again, 14 (56%) had at least one intrauterine pregnancy and 3 (12%) had a repeat extrauterine pregnancy. Twenty-six of the women with a solitary tube desired pregnancy, 12 (46%) of them had at least one intrauterine pregnancy, and 10 (38·5%) had a repeat extrauterine pregnancy. It was concluded that the incidence of intrauterine pregnancy after conservative surgery in patients with both tubes present is not lower than after radical surgery, and that the incidence of extrauterine pregnancy is not higher. The intrauterine pregnancy rate in patients with a solitary tube is high and still higher than the best results available with in-vitro fertilization and embryo transfer. Therefore conservative surgery is indicated in these patients despite the high incidence of repeat extrauterine pregnancy. Since most of the patients who conceived did so during the first year following the operation, we recommend that patients try to conceive immediately.

Although the natural history of extrauterine pregnancy has not changed throughout the centuries, the clinical presentation and approach to treatment have changed dramatically. Before surgical management was used, Parry & Lea (1876) reported a mortality rate of 69%. A major breakthrough was achieved by Tait (1884) when he first performed salpingectomy, and thereby significantly reduced the mortality rate; this operation became and remains the classical treatment for ectopic pregnancy.

Stromme (1953) first described a surgical procedure in which the gestation sac was removed without salpingectomy. This conservative approach did not become popular, but is more acceptable today because the gynaecologist deals with a completely different clinical picture of extrauterine pregnancy, following earlier diagnosis as a result of tests for β-hCG (human chorionic gonadotrophin), ultrasound, and widespread use of diagnostic laparoscopy. This has resulted in a significantly decreased incidence of ruptured extrauterine pregnancy enabling the gynaecologist to perform conservative tubal surgery. Because of the significantly decreased reproductive performance after salpingectomy (Franklin *et al.* 1973; Douglas *et al.* 1969; Shenker *et al.* 1972; Ploman & Wicksell 1960; Timonen & Neiminen 1967), we have examined the merits of conservative surgery as an alternative procedure.

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Subjects and methods

The hospital charts of 58 patients with extrauterine pregnancies who were treated with conservative surgery in the Sheba Medical Center between January 1981 and June 1986 were reviewed. In 30 patients both tubes were present at the time of surgery. The remaining 28 patients had surgery on a single patent tube. In 22 patients the contralateral tube had previously been excised, in three the contralateral tube had undergone hydrosalpinx formation which was not corrected at the time of surgery for ectopic pregnancy and the remaining three patients had had a conservative operation for a previous extrauterine pregnancy in the contralateral tube. These last three were also considered as 'single tube' patients.

The mean age of the patients was 27·4 years (range 20–36) and mean gestational age was 7·5 weeks (range 4–11). No patient had a ruptured extrauterine pregnancy at the time of the operation. In 46 patients the pregnancy was found at the ampullary isthmic junction, in the fimbriae of six patients and in the isthmus of six patients. Nineteen patients (32·7%) were primigravidae. Eight patients had a previous tuboplasty due to past tubal infections. Twenty-three patients had a previous extrauterine pregnancy; 20 had a salpingectomy, and three conservative surgery. Another 10 women had previous pelvic surgery for various reasons, including salpingectomy in two cases. Follow-up ranged from 6 to 66 months, averaging 23 months.

Surgical techniques

Microsurgical principles including continuous irrigation, gentle tissue handling, and meticulous haemostasis using bipolar coagulation were practised during the operation. (For appropriate patients, the Carl Zeiss operating microscope No. 6D with foot panel controls for focus and magnification was used.) In 42 women, dorsal salpingotomy was performed. A 1·5–2·5 cm linear incision was made along the antimesenteric border above the gestational bulge, with the microelectrocautery needle using the operating microscope. The pregnancy and blood clots which extruded through the opening were removed. The placenta was carefully separated from the tubal wall. Bleeding points were controlled with microbipolar coagulation. Meticulous haemostasis was achieved following injection of 5 units of synthetic oxytocin and a 1% solution of 1/1000 epinephrine in normal saline into the tubal wall. The incision was closed in one layer avoiding the mucosa using interrupted nylon 8-0 sutures.

In 11 women tubal abortion occurred. The tube was 'milked' gently, squeezing the gestation sac through the fimbria. In five patients the portion of the tube containing the pregnancy was excised, in two patients re-anastomosis was performed immediately, and in three patients re-anastomosis was performed electively. Re-anastomosis was performed in two layers under the operating microscope. Five to six interrupted 8-0 nylon sutures were placed around the perimeter of the tube through the myosalpinx excluding the endosalpinx. The serosa was then repaired with several interrupted 8-0 nylon sutures. Hydrocortisone (2 g) was instilled into the abdomen before closure Each patient received ampicillin, 1 g three times daily for 5 days postoperatively. There were no postoperative complications.

Results

Of the 58 patients operated upon 51 desired pregnancy and seven used contraceptives. Four patients lost to follow-up were considered as desiring pregnancy. Of the 51 women 36 (70·5%) conceived again at least once, 15 (29·4%) did not conceive. Twenty-six women (51%) had at least one intrauterine pregnancy and 13 women (25·5%) had a repeat extrauterine pregnancy (three women had an intrauterine pregnancy preceding their repeat extrauterine pregnancy). Only the first pregnancy after operation, whether intrauterine or extrauterine was considered in this analysis.

Of the women who desired pregnancy 38 underwent dorsal salpingotomy; 28 of these conceived, 19 had an intrauterine pregnancy and nine had a repeat extrauterine pregnancy. Nine women underwent milking of the tube; four had an intrauterine pregnancy, and three had a repeat extrauterine pregnancy. Four women underwent resection with end-to-end anastomosis; three had an intrauterine pregnancy and one had a repeat extrauterine pregnancy (Table 1). There was a total of 35 intrauterine pregnancies in 26 patients; 25 of the pregnancies were delivered at term, and eight miscarried in the first trimester; two patients are still pregnant.

Table 1. Results of conservative microsurgery for tubal pregnancy and type of operation

Type of operation	Women operated	Women desiring pregnancy	Women with intrauterine pregnancy (%)	Women with repeat extrauterine pregnancy (%)
Dorsal salpingotomy	42	38	19 (50·0)	9 (23·7)
Milking the tube	11	9	4 (44·4)	3 (33·3)
Resection of the tube with end-to-end anastomosis	5	4	3 (75·0)	1 (25·5)
Total*	53	51	26 (51·0)	13 (25·5)
As percentage of women who conceived			(66·7)	(33·3)

* Thirty-six women conceived, three of them had an intrauterine pregnancy prior to their repeat extrauterine pregnancy.

Of the 17 patients with both tubes present who conceived, 73·3% conceived during the first year after the operation. No patient conceived after 2 years and 8 months. Of the 22 patients with a single tube who conceived, 54·5% conceived during the first year. All patients who conceived did so within 3 years and 3 months after the operation (Fig. 1).

Eighteen women underwent hysterosalpingography to investigate subsequent infertility; in 17 (94·4%) the tube operated on was patent, in one the tube was blocked at the site of the operation. Seven women underwent laparoscopy for infertility after the operation; in six the tube operated on was patent with free spillage of dye into the peritoneal cavity. In five patients peritubular adhesions were found. All these seven women underwent a previous hysterosalpingography and the tube operated on appeared patent.

Discussion

Extrauterine pregnancy can be operated on conservatively preserving the affected tube without reducing the likelihood of a subsequent intrauterine pregnancy or increasing the risk of repeat extrauterine pregnancy. Table 2 summarizes the results reported in the literature of 442 patients operated upon conservatively (Timonen & Neiminen 1967; Langer *et al.* 1982; DeCherney & Kase 1979; Jarvinen *et al.* 1972; Stromme 1973; Skulj *et al.* 1964). Most patients had both tubes present; 45·5% had a subsequent intrauterine pregnancy and 11·5% had a repeat extrauterine pregnancy. Our results are similar: in 25 patients with both tubes present, the intrauterine pregnancy rate was 56% and the repeat extrauterine pregnancy rate 12%. Neither of these results differs significantly from those reported after radical surgery In 1630 reported cases (Franklin *et al.* 1973; Douglas *et al.* 1969; Shenker *et al.* 1972; Timonen & Neiminen 1967; Abrams & Farell 1961; Vehaskari 1960), summarized in Table 2, there were 40·9% intrauterine and 14·2% extrauterine pregnancies. Extreme variations exist in the reported intrauterine and repeat extrauterine pregnancy rates

Table 2. Results of radical and conservative surgery for extrauterine pregnancy collected from the literature

	Women desiring pregnancy	Women with intrauterine pregnancy (%)	Women with repeat extrauterine pregnancy (%)
Radical surgery	1630	667 (40·9)*	231 (14·2)*
As percentage of women who conceived		(74·3)	(25·7)
Conservative surgery	442	201 (45·5)*	51 (11·5)*
As percentage of women who conceived		(79·8)	(20·2)
Present study (both tubes present)	25	14 (56·0)*	3 (12·0)*
As percentage of women who conceived		(82·4)	(17·6)

* $P > 0 \cdot 05$.

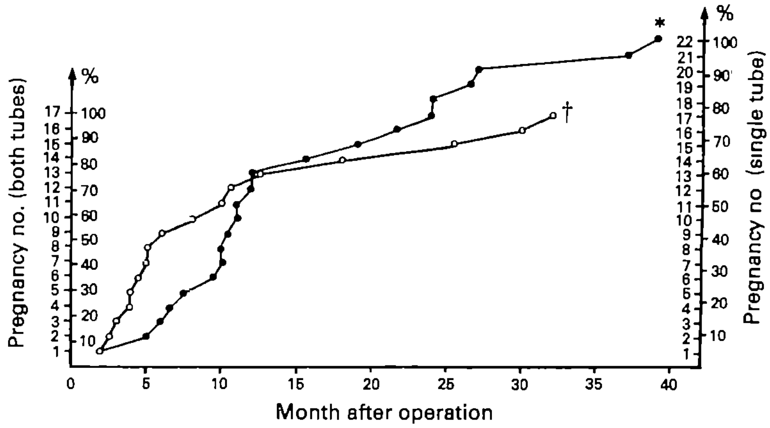

Fig. 1. Cumulative pregnancy rate in 36 patients with either one or two tubes. (Three patients had an intrauterine pregnancy before their repeat extrauterine pregnancy.) ●, One tube; ○, two tubes. *v. † $P<0{\cdot}05$.

(DeCherney 1986) probably as a result of the different ways of calculation. In Table 2 the pregnancy rates were calculated using the two denominators which we believe should be used: (i) the number of women desiring pregnancy; and (ii) the number of women who conceived following surgery. Before surgery or in early pregnancy following surgery a patient should be counselled with both figures in mind.

In view of these results, the growing trend towards conservative surgery seems justified. Nevertheless, these results do not appear to us to reflect the true functional integrity of a tube previously operated upon. We found a high repeat incidence of extrauterine pregnancies (38·5%) in women with a single tube operated upon conservatively (Table 3). Other authors (DeCherney *et al.* 1982) also claim a higher repeat extrauterine pregnancy rate in patients with a single tube than after radical surgery, i.e. salpingectomy for a first extrauterine pregnancy. It is, therefore, interesting that there is no significant difference in the repeat extrauterine pregnancy rate after salpingectomy or conservative surgery in women with both tubes present. There should be a higher extrauterine pregnancy rate after conservative surgery as some ova are fertilized in the tube previously operated upon. It is possible that the similar pregnancy rates are due to a shorter follow-up period after conservative surgery.

There is considerable controversy about the type of operation which should be performed. DeCherney & Kase (1979) and DeCherney *et al.* (1982) perform salpingostomy (without closure). Langer *et al.* (1982), Bukovsky *et al.* (1979) and Sherman *et al.* (1982) perform salpingotomy (with resuture), and Suchet *et al.* (1979) prefer resection and re-anastomosis as a one-stage procedure. In our series of 58 patients, 42 underwent dorsal salpingotomy, 11 milking, and 5 resection and end-to-end anastomosis. There was no statistically significant difference in the intrauterine and extrauterine pregnancy rates following the three different types of operation, although the number of patients under-

Table 3. Fertility following conservative surgery in women with either one or two tubes

	Women desiring pregnancy	Women with intrauterine pregnancy (%)	Women with repeat extrauterine pregnancy (%)
Both tubes	25	14 (56·0)	3 (12·0)
Single tube*	26	12 (46·1)	10 (38·5)
Total	51	26 (51·0)	13 (25·5)

* Three women had an intrauterine pregnancy before their repeat extrauterine pregnancy; in six women the contralateral tube was present, three had undergone hydrosalpinx formation, and three had a conservative operation for a previous ectopic pregnancy.

Table 4. Ectopic pregnancy with one solitary tube; results of conservative macro- and microsurgery

Procedure	Women desiring pregnancy	Women with intrauterine pregnancy (%)	Women with repeat extrauterine pregnancy (%)
Macrosurgery	27	16 (59)*	7 (26)*
Microsurgery	63	37 (59)*	14 (22)*

* $P>0{\cdot}05$

going each operation was relatively small. No recommendation can be made at this time as to the operation of choice which can only be determined by a prospective randomized study. Such a study should be comprised of patients with a single tube to eliminate any doubt as to through which tube the subsequent pregnancy was transported. In our series, there were 26 patients with a single tube desiring pregnancy; 46·1% had an intrauterine pregnancy and 38·5% had a repeat extrauterine pregnancy (Table 3). This is a very high incidence of repeat extrauterine pregnancy, but if future spontaneous pregnancy is desired in this very high-risk population there is no other available alternative. In-vitro fertilization and embryo transfer is the only treatment following bilateral salpingectomy, but the pregnancy rate following this procedure is still much lower than after conservative surgery for extrauterine pregnancy. In our series the operating microscope was used for all procedures except milking. This is not the only technique available, however, macrosurgery may give similar results. Reviewing the literature, we found 27 cases with a single tube who were operated on conservatively using macrosurgical techniques (Ploman & Wicksell 1960; Stromme 1973; Vehaskari 1960; Valle & Lifchez 1983), and 63 similar cases where microsurgical techniques were applied (DeCherney *et al.* 1982; Suchet *et al.* 1979; Oelsner *et al.* 1984). There was no statistically significant difference in the intrauterine and extrauterine pregnancy rate between the two groups of patients (Table 4). To determine if macrosurgery or microsurgery is preferable a prospective randomized study should be designed for one surgeon operating in one centre.

The cumulative pregnancy rate as demonstrated in Fig. 1 shows that there is a statistically significant difference in the time interval between operation and conception for patients with both or only a single tube. Of the patients with both tubes 70·5% conceived within 1 year of operation compared with 59% of the patients with a single tube ($P<0{\cdot}05$—Mann–Whitney *U*-test). This significant difference may be due to ovulation occurring in the ovary with no adjacent tube.

In 18 women with infertility of at least 6 months duration after undergoing surgery, a hysterosalpingogram was performed. The tube which was operated upon was patent in 17 of the 18 patients, only one had a blocked tube at the site of operation. Nevertheless, seven women had a repeat extrauterine pregnancy despite tubal patency, and another seven women desiring pregnancy did not conceive at all, which demonstrates that hysterosalpingography is of little value in the prediction of tubal function. Its only value is in cases in which the tube after operation is totally blocked. In our series only one such case was found. Our conclusion is to wait at least 18 months before performing hysterosalpingography.

This study confirms that the incidence of intrauterine pregnancy after conservative surgery is not lower than after radical surgery and the incidence of extrauterine pregnancy is not higher in patients with both tubes present. In order to preserve fertility, maximum conservation of reproductive organs is desirable since repeat extrauterine pregnancy in the contralateral tube may rupture. In our opinion conservative surgery is the treatment of choice for extrauterine pregnancy in the following patients: nulliparae, women desiring further pregnancy, those with factors causing mechanical infertility in the contralateral adnexa, and those with a single tube.

Acknowledgments

The authors wish to thank Mr Michael Oelsner for his technical assistance and Mrs Judith Lev for preparation of the manuscript.

The work was supported by the Floersheim Foundation.

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Received 16 December 1986
Accepted 18 February 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp 1084–1088

Thyroid function in trophoblastic disease

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Summary. Human chorionic gonadotrophin (hCG) levels and thyroid function were monitored in 44 patients receiving chemotherapy for treatment of trophoblastic disease. We observed a strong correlation between hCG and thyroid stimulating hormone (TSH) concentrations measured by radioimmunoassay, and this appears to be due to cross-reactivity between hCG and the anti-TSH antibody used. The concentration of thyroid hormones was little affected by the raised levels of TSH or hCG, except when the concentration of the latter rose to high levels, usually above 100 000 i.u./l. The possible mechanisms of thyroid homeostasis in trophoblastic disease are considered.

There is debate about the mechanism underlying the well-established observation that measured serum TSH concentrations are raised in women with raised hCG levels. This occurs both in normal pregnancy (Smith & Bold 1983; Weeke *et al.* 1982) and trophoblastic disease (Kenimer *et al.* 1975). There is disagreement about whether the thyrotrophic immunoactivity is due to hCG itself (Kenimer *et al.* 1975) or to some other substance (Amir *et al.* 1984). A similar disagreement exists as to whether this immunoactivity results in the increased secretion of thyroid hormones (Amir *et al.* 1984; Nisula & Taliadouros 1980; Norman *et al* 1981; Nagataki *et al.* 1977). An analysis of results obtained from patients with trophoblastic disease referred to this unit over a period of 3 years (1983–1986) is reported.

Patients and methods

The investigation included 44 patients registered with the Sheffield and Region Endocrine Investigation Centre with a diagnosis of molar pregnancy. In all patients the initial diagnosis was confirmed histologically from tissue obtained at the time of currettage. In each of these patients the hCG level remained elevated, and chemotherapy was necessary. First-line therapy was methotrexate with folinic acid rescue, but patients who failed to respond, or who relapsed, were changed to second-line (actinomycin, vincristine and cyclophosphamide) or third-line (etoposide or Einhorn) regimens. These regimens are a modification of those described by Bagshawe (1969).

The activity of the disease was monitored in all the patients by measurement of serum hCG levels. TSH, total thyroxine (T4) and total tri-iodothyronine (T3) were measured at various times during treatment, which was continued until the serum hCG concentration fell to undetectable levels (< 10 i.u./l).

T4, T3, TSH and hCG were assayed in serum by unpublished standard in-house labelled-antigen radioimmunoassay procedures. All samples and standards were assayed in duplicate. For the T3 and T4 assays bound hormone was separated from free hormone by a second antibody technique and for the TSH and hCG assays by a procedure utilizing donkey anti-rabbit coated cellulose (SAC-CEL, Wellcome Diagnostics, Dartford, Kent, UK). In the hCG assay, the antibody was to the beta chain of hCG.

Thyroxine-binding globulin (TBG) was assayed using a kit supplied by Ciba-Corning

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Table 1. Radioimmunoassay precision data

Assay	Dose	Coefficient of variation (%) Within batch	Between batch
TSH	1·6	12·5	12.5
	8·6	9·3	15·1
	25·0	9·6	9·2
T4	25·0	5·6	6·4
	86·3	3·8	3·1
	166·0	5·4	7·8
T3	0·6	14·2	14·2
	2·9	3·4	3 4
	5·7	3·5	3·5
TBG	15·7*	6·3	7·0
	32·1*	4·0	10·9
	18·9†	6·3	10·0
β-hCG	18·0	13·3	14·4
	38·0	9·2	7·3
	94·8	5·4	9·1

* Controls supplied by manufacturer, no pre-dilution
† Commercial control serum (pre-dilution as for patient samples)

Diagnostics Ltd (Halstead, Essex, UK), according to the protocol described by the manufacturer.

Precision data for the assays are given in Table 1. Internal quality control sera were used in all assays, and performance checked by participation in the UK National External Quality Assurance Scheme.

Highly purified hCG (batch no. 75/537—the first International Reference Preparation, 1975) was obtained from the National Institute for Biological Standards and Controls, Mill Hill, London, UK.

Cross-reactivity of this hCG in the TSH assay was assessed by adding increasing amounts of hCG to a human thyrotoxic serum and assaying for TSH activity. Cross-reactivity was similarly measured in an immunoradiometric assay using monoclonal antibody (Pharmacia AB, Uppsala, Sweden).

Results

The 44 women started on chemotherapy during the period of the study achieved remission (hCG below 10 i.u./l) by August 1986. All of these are included in the following analysis. None of the patients had clinical evidence of hyperthyroidism at presentation. Generally the patients were asymptomatic, but some patients with metastatic disease, particularly those with pulmonary involvement, were often acutely ill before the start of treatment.

The duration of treatment was usually between 2 and 6 months (mean 3·2 months). The mean duration was 4·1 months for patients with initial serum hCG concentrations above 100 000 i.u./l compared with 2·6 months for patients with initial levels below 1000 i.u./l (Table 2). Both hCG and TSH concentrations tended to decline throughout treatment, whereas T3 and T4 concentrations fluctuated. The time-course of the change in concentration of the four analytes during treatment of one of the patients, shown in Fig. 1, is typical.

The correlation between hCG and TSH was confirmed by a log/log scatter plot (Fig. 2). Although the data give a Pearson correlation coefficient of 0·86, the plot suggests that the relation is not linear, even after log transformation, and may be biphasic.

The cross-reactivity of hCG in the TSH assay was investigated, and it was found that the hCG did cross-react significantly with the antibody to TSH used in the assay (Fig. 3). The degree of cross-reactivity was sufficient to account for

Table 2. hCG, TSH, T4 and T3 changes during chemotherapy

Initial hCG concentration (i.u./l)	No. of patients	Mean duration of treatment (months)	Mean fall in serum concentration during treatment hCG (i.u./l)	TSH (mi.u./l)	T4 (nmol/l)	T3 (nmol/l)
10–10^3	16	2·6	262	0·6 ($n=14$)	3 9	−0 19†
10^3–10^4	15	3·3	3370	1·1*** ($n=11$)	7·9	0 30**
10^4–10^5	9	3·5	50 200	8·9*** ($n=8$)	23 3*	0·18
>10^5	4	4·1	435 000	14·0** ($n=4$)	92·0***	1·15

† Negative value indicates a rise in mean serum concentration.

Significance of difference between first and last measurements (Student's *t*-test for paired data without log transformation) *$P<0·02$; **$P<0·01$, ***$P<0·001$.

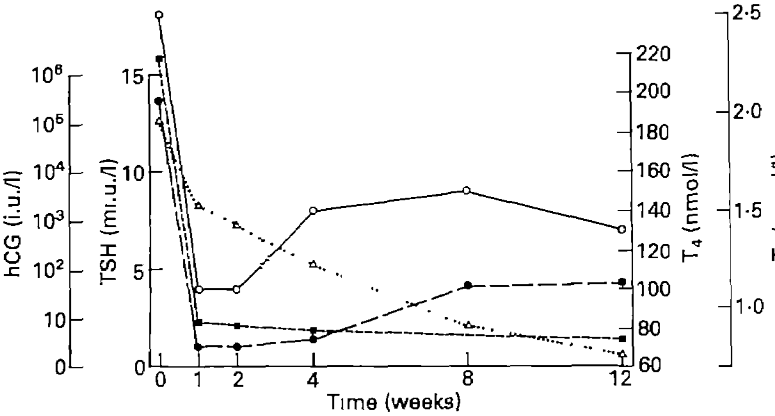

Fig. 1. Changes in hCG (···△···), TSH (– –■– –), T3 (—○—) and T4 (–·–●–·–) during methotrexate therapy in one patient with initially high hCG levels

most or all of the rise in measured TSH levels observed in patients with trophoblastic disease. Furthermore, using a radioimmunometric assay, there was almost no detectable cross-reactivity (Fig. 3).

The correlation between hCG and T3 or T4 (Fig. 4) is much less marked than between hCG and TSH. The Pearson correlation coefficients for T3 and T4 against log hCG were 0·57 and 0·54 respectively. For TSH against T3 and T4 the correlation coefficients were 0·52 and 0·69 respectively. Except at very high levels of hCG, the concentrations of thyroid hormones were not markedly higher than normal.

The changes in levels of hCG, TSH, T4 and T3 during treatment are shown in Table 2. Values at the time of the first serum hCG measurement have been compared with those measured after the serum hCG level had fallen to below 10 i.u./l. The 44 patients have been divided into four groups according to the first measured serum hCG level, and paired *t*-testing was performed on changes in analyte concentrations within each group.

Free T3 and free T4 concentrations were not measured in this study, but we have not observed any significant correlation between hCG concentration and TBG concentration (TBG concentration = 29–34 mg/l for hCG concentrations of 238–91 450 i.u./l).

Discussion

These results confirm the relation between hCG levels and apparent TSH levels measured by standard radioimmunoassay techniques in patients with trophoblastic disease. They suggest that above a serum hCG level of 1000 i.u./l there is a direct log/log correlation. The studies with purified hCG suggest that the raised TSH levels are due to cross-reaction of the anti-TSH antibody with hCG in the radioimmunoassay used for TSH. Nevertheless, the possibility cannot be ruled out that another peptide present in the purified hCG preparation is responsible for the cross-reactivity shown in Fig. 3. Initial tests suggest that this cross-reactivity is not significant in the immunoradiometric assay used, and it would clearly be of great interest to measure TSH in sera from patients with trophoblastic disease by this method

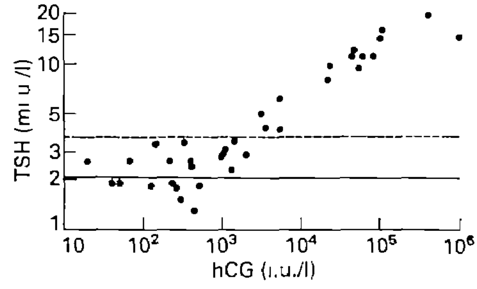

Fig. 2. Plot of log of TSH concentration on log of hCG concentration Each point represents values for an individual subject at the time of the first serum hCG estimation (In some subjects chemotherapy had been started previously on the basis of raised 24-h urinary hCG excretion.) The horizontal lines show the mean (—) and mean + 2 SD (– – – –) TSH concentrations of all patients at the end of treatment, when serum hCG was < 10 i.u./l. Data for 7 of the 44 patients are not available because serum TSH was not estimated initially; their mean initial serum hCG was 6250 i.u /l (range 48–18 300)

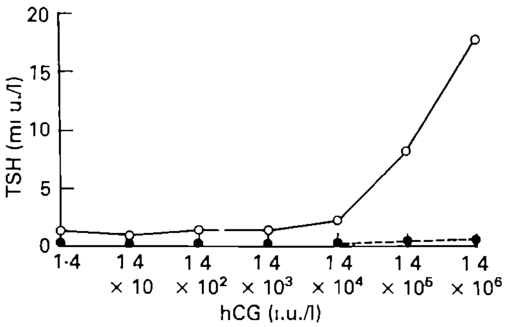

Fig. 3. Cross-reactivity of hCG in the TSH radioimmunoassay. The measured TSH concentration resulting from assaying dilutions of hCG in pooled thyrotoxic serum using our standard radioimmunoassay (—O—) and using a radioimmunometric assay technique (– –●– –) is plotted against the hCG concentration.

The homology of hCG with TSH (Garrett & Kurtz 1986), which could result in the observed cross-reactivity, might also be expected to exert a thyrotrophic effect. However, the correlation between either hCG or TSH levels and thyroid hormones was poor except at very high levels of trophic hormone. A possible explanation for this is that the immunoreactive material measured in the radioimmunoassay for TSH has two components, namely true TSH and other immunoreactive peptides, mainly hCG. It is likely that native TSH is a more potent thyrotrophic substance than immunoequivalent amounts of other immunoreactive components. Thus when hCG is present, TSH measurements using a standard radioimmunoassay are likely to overestimate the thyroid drive present. As the hCG concentration rises, thyroid homeostasis could be initially maintained by feedback inhibition of the native TSH. After complete suppression of the native TSH this mechanism would no longer be available, and further increases in hCG could result in a rise in thyroid hormone levels. It should be possible to test this hypothesis by more specific measurement of native TSH, such as appears to be offered by immunoradiometric methods. However, in the same way that the standard radioimmunoassay probably overestimates the thyrotrophic activity present, such specificity may result in an underestimate of thyrotrophic activity.

In our study, symptoms of thyrotoxicity were not observed, even when there was biochemical evidence of increased thyroid activity. This is in agreement with a previously reported finding that in most cases of biochemically demonstrated hyperthyroidism in association with trophoblastic disease, symptoms of thyrotoxicosis do not occur (Odell *et al.* 1963; Nagataki *et al.* 1977; Amir *et al.* 1984). In contrast, a high incidence of symptoms of thyrotoxicity among African women with trophoblastic disease has been reported (Norman *et al.* 1981).

Pregnancy is another condition in which high hCG levels occur. It has been proposed that hyperemesis gravidarum is associated with thyrotoxicosis (Jeffcoate & Bain 1985; Valentine *et al.* 1980), and that this may be caused by raised levels of TSH-like material secreted from the placenta (Brunn & Kristofferson 1978).

It is not clear why some subjects with high

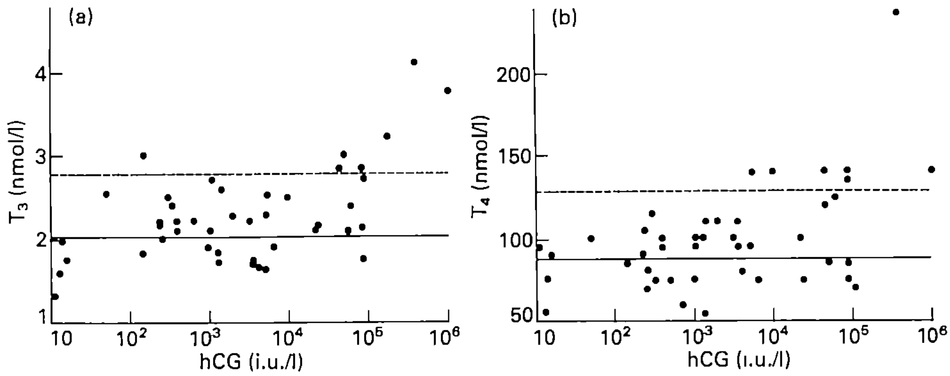

Fig. 4. Plot of T3 (a) and T4 (b) concentrations on log of hCG concentration. Each point represents values for an individual subject at the time of the first serum hCG estimation. (In some subjects chemotherapy had been started previously on the basis of raised 24-h urinary hCG excretion.) The horizontal lines show the mean (——) and mean + 2 SD (– – –) T3 or T4 concentrations of all patients at the end of treatment, when serum hCG was < 10 i u./l.

hCG levels and raised total T3 and T4 concentrations present with clinical hyperthyroidism and some do not. It is possible that the concentrations of total thyroid hormone do not reflect the concentrations of free hormone, but TBG levels are similar in pregnancy (Franklyn *et al.* 1983) to those we observed in trophoblastic disease. Factors other than the concentrations of thyroid hormones may be responsible. For example, it has been suggested that oestrogens may sensitize the response to thyroid hormones during pregnancy (Franklyn *et al.* 1983).

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Received 24 November 1986
Accepted 17 March 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp 1089–1093

Treatment of cervical intraepithelial neoplasia (CIN) by radical electrocoagulation diathermy: 5 years' experience

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Summary. During the first 5 years of a colposcopy clinic established in a London teaching hospital 653 new patients were seen, usually referred because they had had an abnormal cervical smear report suggesting cervical intraepithelial neoplasia (CIN). Of 490 women treated within the district for CIN, 361 (73·7%) underwent radical electrocoagulation diathermy, 91 (18·6%) were treated by cone biopsy, 34 (6·9%) underwent hysterectomy and the other four patients were treated by cryocautery. Of the 245 women treated by radical electrocoagulation diathermy who have been followed for at least 12 months, persistent or recurrent disease has been found in only 15, a first time treatment success rate of 93·9%.

Over the last 10 years there has been an alarming increase in the number of young women presenting with abnormal smears suggestive of cervical intraepithelial neoplasia (CIN) (Wolfendale *et al.* 1983). Cone biopsy, because of its inherent operative morbidity and a recognized complication rate in subsequent pregnancies (Jones *et al.* 1979), is now considered overtreatment for the majority of patients although it still has a significant role. Colposcopy and local destruction is the treatment of choice for the young patient with CIN (Singer & Walker 1982).

There are four principal methods of local destruction available for the treatment of cervical premalignancy—cryotherapy, laser ablative therapy, 'cold' coagulation and radical electrocoagulation diathermy (RED) (Singer & Walker 1985). Most experience with the 'cold' coagulator has been reported from Tayside (Duncan 1982, 1983) and there are now many reported series on treatment using cryotherapy (Townsend & Ostergard 1971; Townsend 1979; Creaseman *et al.* 1981) and laser ablation (Bellina *et al.* 1981; Jordan & Mylotte 1982; Anderson 1982). Apart from the series reported from Melbourne by Channen & Rome (1983) and one small series reported in the UK (Woodman *et al.* 1985), there are few series reporting the use of electrocoagulation diathermy as local destruction for CIN.

In April 1981 a colposcopy service was established at the Royal Free Hospital as a response to the increasing number of referrals being received from general practitioners and family planning clinics of young women with abnormal cervical smears During the 5 years that this clinic has been in operation the principal method of local destruction employed by the singlehanded sole colposcopist (P A.F.C.) has been radical electrocoagulation diathermy. Details of the records of the 653 women seen in the clinic during this period have been examined and are reported here.

Patients and methods

In the first 5 years of the clinic from April 1981, 653 new patients were referred to the colposcopy

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clinic either because they had had a cervical smear suggesting CIN, because they had a 'suspicious' cervix, or because they had been treated for CIN elsewhere and had been referred for assessment and follow-up. The number of new patients seen has risen from 96 in the first year to 378 in the sixth year. The increasing trend in referrals is continuing and approximately 82% of patients referred in any one year have a diagnosis of CIN.

Patients underwent a standard colposcopic examination and any abnormal areas (Walker *et al.* 1983) were biopsied, the tissues were fixed in formalin and sent to the histology laboratory for sectioning, staining and reporting (Buckley *et al.* 1982).

Treatment

If a diagnosis of CIN was made the patient was treated by either local destructive techniques, usually RED, cone biopsy or hysterectomy as indicated in accordance with standard colposcopy practice (Singer & Walker 1982). If there was no evidence of suggestive pathology the patient was recommended for follow-up by cervical cytology with or without further colposcopic assessment.

Diathermy

Patients suitable for treatment by electrocoagulation diathermy were admitted to the hospital for treatment under general anaesthesia. The technique employed was similar to that described by Chanen & Hollyock (1971). Examined under anaesthesia in the lithotomy position the cervix was displayed using an insulated Auvard's speculum. Colposcopy was not repeated before RED as all patients were treated within 3 weeks of their initial colposcopic assessment. Dilatation and curettage was not routinely performed unless indicated for some other suspected gynaecological pathology.

The area to be destroyed was delineated using Lugol's iodine. First the needle electrode was used to map out the circumferential margin of treatment 2 mm beyond the Lugol's iodine negative line within normally staining ectocervix. Each insertion of the needle was to a depth of approximately 7 mm in the long axis of the cervix and at intervals of 2 mm. Having delineated the margin of treatment the circumscribed area on the anterior and posterior ectocervix was subjected to multiple insertions of the needle to 7 mm at 2 mm intervals. Second, the spatula electrode was used starting in the lower centimetre of the cervical canal and carried laterally in a series of 10 to 12 shallow radial cuts around the external os to ensure adequate treatment of the squamo-columnar junction. Finally the ball electrode was used to ensure complete destruction of the transformation zone.

The aim was to destroy tissue to the depth of 7 mm, hence the term radical electrocoagulation diathermy, to make the distinction between this form of therapy and that of superficial cervical diathermy or cautery, neither of which is appropriate treatment for CIN.

Postoperatively the patients were advised to refrain from sexual intercourse for a period of 6 weeks. For the first 10 nights sultrin cream was inserted into the vagina both to prevent infection and also to create an acid environment which would encourage the new squamo-columnar junction to form in the endocervix rather than on the ectocervix. The patients were cautioned to expect a bloodstained vaginal discharge for up to 2 weeks followed by a serous discharge for a further 10–14 days. On discharge from hospital each patient was given a follow-up outpatient appointment at 3 months after surgery. At this visit the cervix was examined and a cervical smear taken. After this the patient was seen on three further occasions at 3-month intervals and further smears taken. If all cytology was reported as normal, at the end of 1 year of surveillance the patient returned to her general practitioner for further follow-up with a recommendation for annual cervical cytology. If any abnormality was reported on a follow-up cervical smear, the patient was colposcoped again and the appropriate action was taken. Patients were also advised not to become pregnant for 1 year after treatment and until all four follow-up smears had been reported as normal. Patients pregnant at the time of presentation were assessed colposcopically with or without directed punch biopsy. As long as the findings were consistent with CIN, treatment was postponed until after delivery.

Results

Of the original study group of 653 women, 527 (80·7%) had a diagnosis of CIN; 111 (17·0%) had no evidence of CIN or invasive cancer, 11 (1·7%) had invasive cancer and 4 (0·6%) had

Table 1. Patients treated by radical electrocoagulation diathermy: histology and persistence/recurrence

Histology	No. of patients	Lost to follow-up	Persistent/ recurrent disease
CIN 3	125	3	7
CIN 2	54	4	4
CIN 1	53	3	3
Normal*	23	0	1
Total	255	10	15

* Normal (colposcopically and cytologically abnormal).

microinvasive carcinoma. Of the 527 patients with CIN, 490 were treated at the Royal Free Hospital. Of these 365 (74·5%) were treated by local destructive techniques (4 by cryotherapy, 361 by RED), 91 (18·6%) underwent cone biopsy and 34 (6·9%) were treated by hysterectomy.

Of the 361 patients treated by RED in the first 5 years, 255 (70·6%) were treated before August 1985. A further 106 patients treated after this time have not yet completed the first year of follow-up and are therefore not included in this report. The histological diagnosis from the colposcopically directed biopsy of 255 women, later treated by electrocoagulation diathermy, in the study group is shown in Table 1. Ten (3·9%) patients were lost to follow-up, six emigrated and four moved to another health district, of these the nine for whom cytology results are available were cytologically negative at their first follow-up visit. Of the remaining group of 245 women, 15 (6·1%) have required further treatment for persistent/recurrent disease, a first-time treatment success rate of 93·9%. Of the patients with persistent disease 13 were diagnosed in the first year of follow-up, eight of them had abnormal cytology at the first follow-up appointment, five at subsequent visits within the first year. One of the other two treatment failures occurred at 17 months and the other patient became cytologically positive 4 years after treatment; this probably represented a new disease. Table 2 shows a detailed analysis of the persistent/recurrent cases and Table 3 shows details of the follow-up of patients into the second, third and fourth year after treatment for patients living within the health district.

Eleven of the 15 patients with persistent/recurrent disease had lesions which were confirmed by histology as CIN. The other four patients developed cytological abnormalities confirmed colposcopically, but directed biopsies proved negative for CIN. In addition there were four other patients who developed a cytological abnormality during follow-up, but who were

Table 2. Patients requiring re-treatment for persistent/recurrent disease

No	Length of follow-up until diagnosis (months)	Original histology	Subsequent treatment	Final histology
1	3	CIN 3	Cone	CIN 3
2	3	CIN 2	Cone	CIN 2
3	3	CIN 2	RED	Normal*
4	3	CIN 1	Cone	CIN 2
5	3	CIN 1	RED	Normal*
6	3	Normal*	RED	Normal*
7	5†	CIN 3	Cone	CIN 3
8	6	CIN 3	Cone	CIN 3
9	8	CIN 3	Hysterectomy	CIN 3
10	8	CIN 3	RED	CIN 1
11	9	CIN 3	Cone	CIN 3
12	12†	CIN 3	Cone	CIN 3
13	12	CIN 2	RED	Normal*
14	17	CIN 2	Hysterectomy	CIN 1
15	50	CIN 1	Hysterectomy	CIN 1

CIN, Cervical intraepithelial neoplasia; RED, radical electrocoagulation diathermy

* Cytologically and colposcopically CIN.

† First follow-up smear.

Table 3. Long-term follow-up of patients living within the district treated by radical electrocoagulation diathermy

Months since treatment	Total patients followed up	Patients with evidence of persistent/ recurrent disease
12	245	13
13–18	150	1*
19–24	103	0
25–30	72	0
31–36	61	0
37–42	42	0
43–48	29	0
49–54	14	1
55–60	2	0

* Fourth follow-up smear.

found to be colposcopically and histologically normal and who now have normal cytology. These last four patients have not been included as cases of persistence or recurrence.

The following complications occurred in the 255 patients treated by RED Four patients experienced primary haemorrhage, three requiring vaginal packing at the time of the procedure, and a further patient, noted to be bleeding heavily on the day after treatment, was kept in bed for a further day but did not require specific treatment. Two other patients were admitted 2 weeks after treatment with secondary haemorrhage; both were treated with antibiotics and bed rest. No patient required examination in theatre or transfusion. The total haemorrhage rate was 2·4%. Three patients were admitted 3 weeks after treatment with pelvic infection which was treated with antibiotics and bed rest. In addition two patients experienced superficial diathermy burns but neither required specific treatment. This is an overall complication rate of 11 (4·3%) in 255 treated patients.

Discussion

There has been an alarming increase in the prevalence of abnormal cervical smears particularly amongst younger women in recent years (Wolfendale *et al.* 1983). In addition evidence is accumulating that suggests that not only is it unlikely that the milder degrees of CIN regress (Campion *et al.* 1986), but also, that a smear report suggesting mild dyskaryosis may well be an underestimate of the true degree of the abnormality. In a recent study from Dundee (Walker *et al.* 1986) nearly 70% of patients referred for colposcopy because of a cervical smear which showed simply 'mild atypia' were found on biopsy to have CIN 3. In this study CIN 3 was found on biopsy in over 12% of patients referred with a smear suggesting CIN 1. All of these factors will inevitably lead to further increasing strains on existing colposcopy services.

It has been recognized for some time now that there is a need for a colposcopy clinic in almost every district general hospital (Jordan 1983) and many such clinics are already in operation (Singer *et al.* 1984). Although some practitioners have reported good first-time treatment success rates with cryotherapy (Richart *et al.* 1980), most reports suggest a persistence/recurrence rate of between 12% and 25% particularly for large CIN 3 lesions (Hatch *et al.* 1981; Wright & Davies 1981). The choice for most clinicians therefore lies between carbon dioxide laser therapy, RED and 'cold' coagulation The initial capital outlay for laser equipment may well be unattainable for many health districts at a time of financial stringency. However, RED offers an effective alternative method of treatment with minimal complications and a first-time treatment success rate of greater than 93%, rivalling, indeed surpassing, that reported in most series of laser treatment. Hollyock *et al.* (1983) reported from a large series of patients that there were no important short- or long-term pregnancy-associated complications after treatment by RED. The advantage of RED is that once the important essential of a trained colposcopist has been satisfied, a method of treatment is immediately available in the operating department of any general hospital.

The patients in this series were followed up for at least 1 year in the gynaecology clinic with cervical smears every 3 months. It was not possible routinely to colposcope follow-up patients as the colposcopy clinic was overstretched in providing a service for new patients with untreated disease. There is a theoretical disadvantage in this in that the clinician can never be quite sure that the new squamo-columnar junction will be readily accessible for follow-up cytology. Hollyock *et al.* (1983) have suggested that the new squamo-columnar junction may not be visible in as many as 60% of patients after treatment, but Woodman *et al.* (1985) suggest a proportion of 30%. One alternative strategy to deal with this potential problem is to colposcope each patient 4 months after therapy, and if the new squamo-columnar is seen to be readily accessible, to follow up the patient thereafter by cytology alone. If, however, the junction is not seen the patient should be followed up by both cervical smears and endocervical brushes. The results from this study would suggest that most of the patients with persistent/recurrent disease will be found within the first year of follow-up, and if the patients are free of disease at that time they may return to their general practitioner for annual cytological screening.

Acknowledgments

We would like to express our thanks to Sister F. Williams for all her help in the colposcopy clinic and to Miss P. Taylor for her help in retrieving patient records.

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Received 6 January 1987
Accepted 20 March 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1094–1097

Tissue macrophage response in human papillomavirus infection and cervical intraepithelial neoplasia

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Summary. Tissue macrophages in the uterine cervix were studied immunocytochemically with monoclonal antibody (MoAb) 3.9 which reacts with the majority of macrophages, and E11 which is specific for the C3b receptor, CR1. Samples from five normal women, six with human papillomavirus (HPV) infection and 10 with cervical intraepithelial neoplasia (CIN) were tested. A small population of MoAb 3.9 positive and only occasional MoAb E11 positive macrophages were found in the normal cervix. In HPV infection and CIN there was a significant infiltration of MoAb 3.9 positive and MoAb E11 positive macrophages in both the epithelium and the stroma. The pattern of infiltration in these groups of women suggests that these macrophages were most likely to be functioning as the first line of defence against the spread of the virus infection, either through a direct anti-virus mechanism or non-specific phagocytosis.

The recent findings that Langerhans' cells (Tay *et al.* 1987*a*) and T-lymphocytes (Tay *et al.* 1987*b*), especially the T-helper subset, are depleted in simple human papillomavirus (HPV) infection of the cervix, and also in cervical intraepithelial neoplasia (CIN) associated with HPV infection, indicate that there might be no effective T-cell mediated anti-virus and anti-tumour activity in these conditions. However, the role of tissue macrophages in cervical HPV infection and CIN has not been investigated. Macrophages have a wide range of functions including non-specific phagocytosis, antigen presentation, direct cytotoxicity to virus infected cells or tumour cells, and sometimes inhibition of lymphocyte proliferation (Dougherty & McBride 1984). Macrophage response in the cervix infected by HPV may therefore play an important part in determining the outcome of the infection and the development of CIN and invasive cancer.

In the present study two non-cross-reacting monoclonal antibodies (MoAb) were used to delineate the tissue macrophage response in the cervix with HPV infection and CIN. MoAb 3.9 is specific for the p150,95 molecule found on the majority of monocytes and macrophages (Hogg *et al.* 1986) and MoAb E11 recognizes the C3b receptor, CR1, which has increased expression on stimulated myeloid cells (Hogg *et al.* 1984; Fearon & Collins 1983).

Materials and methods

Tissue preparation

Two adjacent colposcopically directed punch biopsies from the same lesion within the atypical

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transformation zone were obtained from 16 women attending a district colposcopy clinic. Their mean age was 31·2 (SD 6·7) years. Cervical biopsies for the normal control group were obtained from five women who had received at least one normal smear test immediately before the present admission for a minor gynaecological operation unrelated to the cervix. Their mean age was 28·8 (SD 6·9) years. In each case one biopsy was snap frozen in liquid nitrogen and the other fixed in formol sublimate solution for routine histology using the criteria of Buckley *et al.* (1982) and Dyson *et al.* (1984). Cryostat sections from the snap frozen material were prepared as described previously by Tay *et al.* (1987*b*).

Indirect immunocytochemical staining

Immunoperoxidase staining of cryostat sections was performed as described previously (Tay *et al.* 1987*b*) using both MoAbs at 1:1 dilution.

Cell counts

The number of positively stained mononuclear cells within the epithelium and the stroma of the whole section was counted under a light microscope at × 250 final magnification. The sectional areas of the whole epithelium and the stroma were measured with a Mop-videoplan image analyser using a calibrated drawing tube and a digitizing tablet. The results were expressed as the number of cells per mm^2 sectional area.

Statistical analysis

Cuzick's (1985) method for Wilcoxon-type test for trend on non-parametric data was used to test the difference in the macrophage cell counts between the histological groups.

Results

The results of the cell counts per mm^2 sectional area are summarized in Table 1.

MoAb 3.9 staining

In the normal cervix small numbers of macrophages stained with MoAb 3.9 were scattered within the epithelium and the stroma. The cell counts in the stroma were double that within the epithelium. The mean cell counts in the epithelium showed a four-fold increase in HPV infection, a two-fold increase in CIN 1 and only a marginal increase in CIN 3. This trend of difference is statistically significant (P=0·013) In the stroma there was a similar trend with a six-fold increase in HPV infection, a three-fold increase in CIN 1 and a two-fold increase in CIN 3 (P=0·003) in the mean number of macrophages.

MoAb E11 staining

CR1 receptor positive cells were rarely encountered in the normal cervix, either in the epithelium or in the stroma. They were present in all cases of HPV infection and CIN. The cell counts were highest in HPV infection and then declined from CIN 1 to CIN 3. This trend is highly significant both in the epithelium

Table 1. Macrophage cell counts per mm^2 sectional area

	HPV infection (n=6)	CIN 1 (n=5)	CIN 2/3 (n=5)	Normal (n=5)
Epithelial				
3.9+	86·1	46·4	24·9	20·6
	(27·2–183·0)	(9·2–130·4)	(16·4–35·9)	(4·5–61·0)
E11+	21·9	24·4	11·8	0·2
	(1·1–43·5)	(1·0–74·4)	(6·5–19·0)	(0–1)
Stroma				
3.9+	359·3	147·0	113·8	49·3
	(77·5–686·7)	(11·8–276·8)	(58·4–168·3)	(21·7–73·1)
E11+	220·7	134·2	50·5	1·4
	(34·2–500·0)	(10·8–275·0)	(42·5–55·2)	(0–7)

Results are mean macrophage counts with the range in parenthesis.

(P=0·007) and in the stroma (P=0·001). The mean of the ratios of MoAb E11 positive to MoAb 3.9 positive cells in the epithelium was 0·48 in HPV infection, 0·54 in CIN 1, and 0·49 in CIN 3 cases; and 0·63, 0·94 and 0·52 respectively in the stroma. There is no statistical difference in these ratios.

Discussion

We have previously reported the depletion of Langerhans' cells and T-lymphocytes and scarcity of B-lymphocytes in HPV infection and CIN (Tay *et al.* 1987*a*,*b*). The findings in this study therefore indicate that macrophage infiltration constitutes the predominant cellular reaction in these conditions. A selective increase in macrophages has also been observed in colorectal tumours (Allen & Hogg 1985) suggesting that this may be a general phenomenon. Several implications of these cellular infiltrations should be considered:

(1) The finding of a maximal macrophage response in HPV infection and decreasing numbers of macrophages with increasing severity of CIN might suggest that the macrophage infiltration was an early response to viral infection rather than a direct anti-tumour activity against cervical neoplasia (Adams & Snyderman 1979; Norman 1985). This is supported by the similar trend of decreasing prevalence of HPV antigen expression as the severity of epithelial abnormality increases from simple HPV infection to CIN 1 and CIN 3 (Jenkins *et al.* 1986) This might reflect the non-specific scavenger role of macrophages.

(2) The absence of lymphocytic reaction and the reduction of HLA-D region positive cells in HPV infection and CIN (Tay *et al.* 1987*a*) suggest that these macrophages are not antigen presenting cells in the induction of an immune response (Unanue 1981). Indeed, it is possible that they inhibit the proliferation and differentiation of lymphocytes (Noar 1979; Baird & Kaplan 1977) and may be involved in the induction of local immunosuppression.

(3) In some situations, macrophages have been shown to promote tumour growth (Gorelik *et al.* 1982; Prehn 1982; Khadim & Rees 1984). It has also been suggested that activated macrophages might promote neoplastic progression through the ability to induce mutations via reactive oxygen metabolites (Weitzman & Stossel 1981, 1982; Weitberg *et al.* 1983; Fulton *et al.* 1984). Whether macrophages promote the transformation of HPV infected cervical epithelial cells into CIN is unclear and is of great interest and importance.

In this preliminary study it appeared that macrophage infiltration in HPV infection and CIN might be the first line of reaction against HPV infection. Whether this is an effective antiviral response or whether viable virus may persist within macrophages, promoting spread and recurrence of infection, allowing or even promoting the development of CIN, requires further elucidation.

Acknowledgments

We would like to thank the Cancer Research Campaign and Imperial Cancer Research Fund for generous support.

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Received 7 November 1986
Accepted 13 April 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1098–1102

Rescue of menotrophin cycles prone to develop ovarian hyperstimulation

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Summary. In an attempt to prevent the loss of 'overstimulated cycles' associated with human menopausal gonadotrophin (hMG)-induced ovulation, oestradiol levels and ovarian follicular state were monitored in 12 women with 'overstimulated cycles' after withholding hMG for several days. Human chorionic gonadotrophin (hCG) was administered when oestradiol levels were ≤1700 pg/ml and the leading follicles between 17 and 22 mm in diameter. During the withholding period follicular growth continued in all patients, while oestradiol levels declined in all but three. These three patients conceived. Ovulation was observed in six additional women. Ovarian hyperstimulation did not occur in any of the 12 patients. We conclude that a rescue of 'overstimulated cycles' is sometimes possible. Conception seems to depend on a continuing rise of E2 levels and early detection of 'overstimulation'.

The ovarian hyperstimulation syndrome is a severe complication of the use of menotrophins for ovulation induction. Death and severe morbidity have been reported with this syndrome (Moses *et al.* 1965; Engel *et al.* 1972). Ovarian hyperstimulation is related to high oestrogen levels, with or without multiple ovarian follicles ('overstimulated cycles'), at the time of hCG administration (Karam *et al.* 1973; Tal *et al.* 1985). In our experience, ovarian hyperstimulation is likely to occur during menotrophin therapy if there is multifollicular development and plasma oestradiol (E2) levels are >1700 pg/ml (Blankstein *et al.* 1986). In such cases hyperstimulation is avoided if hCG is withheld but this prevents any chance of conception (Blankstein *et al.* 1986). However, since the failure to utilize the treatment cycles for ovulation involves a substantial financial loss to the patient and since their repeated occurrence may ultimately impair the physician–patient relationship, it is desirable to find a way to prevent overstimulation and yet allow a chance of pregnancy.

During the normal menstrual cycle a secondary decrease in FSH induced by negative feedback (diZerega & Hodgen 1981) causes atresia of all recruited follicles but one. If it were possible to imitate this effect, 'overstimulated cycles' might result in safe conception. If the intrinsic gonadotrophic activity were to maintain the growth of only one or two leading follicles when hMG must be withheld because of high oestrogens or because of the development of many premature follicles, then a controlled ovulation could be induced at a later stage of the cycle when few mature follicles are secreting adequate amounts of periovulatory oestrogen.

The object of the present study was to determine whether in 'overstimulated cycles' a con-

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trolled pause between menotrophin administration and hCG injection would influence periovulatory conditions and prevent the loss of the induced cycle.

Patients and methods

Twelve consecutive women with anovulatory cycles, normal FSH and normal or elevated LH levels and intrinsic oestrogenic activity (Group II, WHO classification) (WHO Scientific Group Report 1973) treated with hMG/hCG for ovulation induction were selected from our infertility clinic for participation in this study. All had one of the following criteria for overstimulation: (i) E2 levels >1700 pg/ml (the critical preovulatory limit for the development of overstimulation); (ii) adequate preovulatory E2 levels (<1700 pg/ml) and diameter of leading follicle ≤15 mm; (iii) E2 levels between 700 and 1000 pg/ml with leading follicles ≤11 mm in diameter. hMG administration was withheld in these patients, but observations were continued. Plasma E2 levels and follicular development were assessed daily. If E2 levels became adequate (≤1700 pg/ml) and the diameter of the leading follicle was between 17 and 22 mm, 10 000 i.u. of hCG were given on 2 consecutive days. All the patients had developed overstimulation in previous hMG/hCG cycles and hCG had been withheld. Ovulation was assumed to have occurred if at least two of the following criteria were present: (i) Ultrasound detection of fluid in the cul-de-sac and disappearance of most of the previously diagnosed ovarian follicles on days 1 and 2 after hCG administration; (ii) progesterone levels of ≥20 ng/ml on day 6 or 7 after hCG injection; (iii) a biphasic basal body temperature (BBT) curve.

In all participants mechanical infertility had been ruled out by either hysterosalpingography or laparoscopy. Results of sperm analysis and postcoital tests were normal.

E2 plasma levels were assessed daily by a radioimmunoassay as described previously (Sufi *et al* 1984). Blood for plasma progesterone was separated immediately and stored at −20°C until assayed as described by Sufi *et al.* (1984). Pelvic ultrasound scanning used a real-time sector scanner (Diasonic DRF 20). The largest follicular diameter (lfd) and the diameter perpendicular to it (pfd) were determined. The diameter of each follicle was defined as (lfd+pfd)/2. The mean diameter of all follicles (mfd) was defined as the sum of all the follicular diameters divided by the number of all follicles.

Results

The duration and mean dosage of menotrophin treatment are depicted in Table 1. It can be seen that most patients were given two to three ampoules hMG (75 i.u. FSH and 75 i.u. LH per ampoule) per day for 5–8 days before hMG therapy had to be withheld. The mean follicular diameter continued to rise in all patients despite withholding hMG (Fig. 1). Moreover, the number of follicles did not decrease significantly. On the first day of the treatment pause, a total of 89 follicles >7 mm was recorded in the 12 women (7–8 per woman). On the day of hCG administration there were 80 follicles > 7 mm. Our daily observations suggest that no further ovarian follicles were recruited after hMG was discontinued. Thus, only a few follicles underwent regression (atresia?) Despite the continuing growth of most follicles, plasma E2 levels declined in 9 of the 12 patients from day 1 of the treatment pause until the hCG injection (Fig. 1). In three women with rising E2 levels (700–1000 pg/ml) in whom hMG was discontinued because of slow follicular development (leading follicle ≤11 mm), E2 levels rose proportionally to ovarian follicular growth until the day of hCG administration. All three pregnancies recorded occurred in these three patients (Fig. 1) None of the 12 patients developed ovarian hyperstimulation during the hMG cycles.

Ovulation/luteinization occurred in 9 of the 12 women (Table 2). The interval between the last hMG administration and the first hCG injection ranged from 2–10 days. The data in Table 3 show that all seven women given a treatment pause of 2–4 days ovulated and three of them conceived

Table 1. Duration and dosage of human menopausal gonadotrophin (hMG) therapy

	hMG therapy	
No. of patients	No. of days	Mean no of ampoules/patient*
2	5	12 5
6	6	16
2	7	14
2	8	28·5

* Each ampoule contained 75 i.u. FSH and 75 i.u. LH

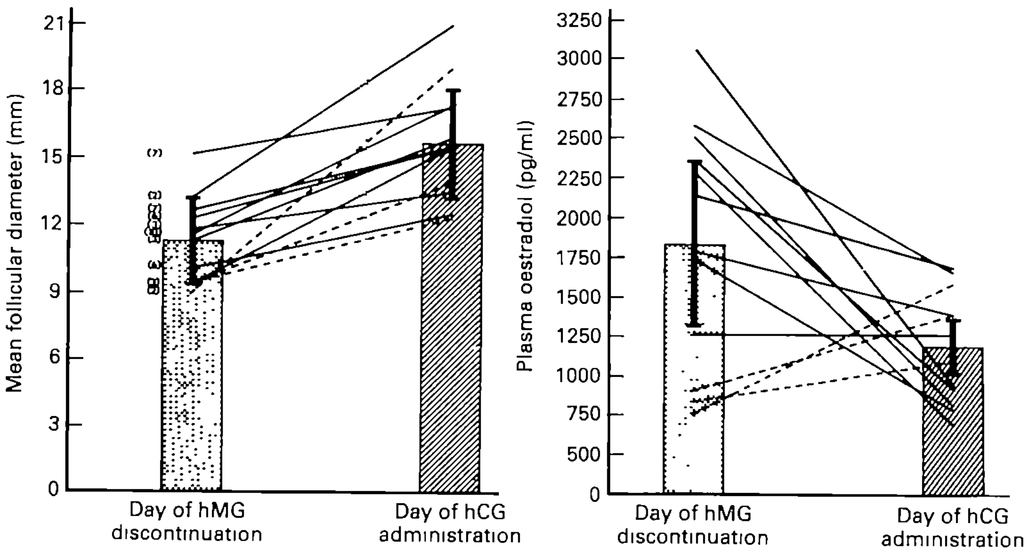

Fig. 1. Individual and mean values ± SD in mean follicular diameter (mm) and plasma oestradiol (pg/ml) at the time of hMG discontinuation and hCG administration in 12 women. (Three women who conceived are marked by a broken line.) The numbers in parenthesis give the number of days between hMG discontinuation and hCG administration for the individual women

during this cycle. Of the five patients given an interval of 6–10 days only two ovulated and none conceived.

Discussion

Monitoring oestrogenic activity and ovarian follicular development during induction of ovulation with menotrophins can prevent the development of ovarian hyperstimulation. Withholding hCG in the treatment cycle has remained the most widely used and recommended measure for the prevention of the syndrome (Blankstein *el al.* 1986; Schenker & Weinstein 1978). Our results suggest that our proposed regimen may lead to the rescue of some of the 'overstimulated cycles' resulting in ovulations and conceptions. Thus, a carefully controlled prolongation of the interval between the last hMG injection and the first hCG administration with daily E2 and ultrasonic examinations provides an alternative to the complete loss of the induced cycle.

In our study nine patients ovulated after injection of hCG, while in the three remaining women vaginal bleeding occurred a few days after hCG administration. Spontaneous ovulation was not observed during the treatment pause in any of the subjects. The longer the pause between hMG discontinuation and hCG administration, the lower was the rate of ovulation and pregnancies (Table 3). The three women who did not ovulate had a pause of ≥6 days while all those with intervals <5 days ovulated. The three pregnancies were achieved after treatment pauses of 3 and 4 days. This suggests the presence of a critical lifespan for the optimal function of the oocytes, as was observed by Levran *et al.* (1985) in an in-vitro fertilization programme where the pregnancy rate was highest if hCG was administered after 6 days of progressive increase in plasma E2 levels. The authors concluded that 6 days of rising E2 levels

Table 2. Ovulation according to plasma progesterone on day 6–7 after hCG injection, ultrasound findings and basal body temperature (BBT)

Ovulation criteria	No of patients
Progesterone (ng/ml)	
<10	3
10–20	1
>20	8
Ultrasound findings	
Negative	3
Positive	9
BBT	
Monophasic	3
Biphasic	9

Table 3. Duration of pause in menotrophin administration and outcome

Duration of pause (days)	No. of patients	Ovulation	Pregnancy
2	1	1	0
3	4	4	1
4	2	2	2
6	2	1	0
7	2	1	0
10	1	0	0
Total	12	9	3

represented a mean optimal period for follicular growth and oocyte maturation in stimulated cycles

Contrary to our expectations, the decrease in gonadotrophic support with hMG at a time of advanced follicular development did not lead to the selection of one or a few 'leading' follicles and the decline of all others. In hMG-stimulated cycles many follicles are recruited and a dyssynchronous follicular development is the rule. It would be of interest to examine whether the observed decrease in plasma E2 was due to a gradual decline in the oestrogenic secretion of all follicles, or whether some of the follicles continued to perform well while others became atretic. Such a course of events could explain the observed disparity between the number of follicles and the plasma oestrogens. Laufer *et al.* (1984) reported that delaying hCG in hMG-induced cycles in women with normal cycles decreased the fertilization rate. Women who received hCG 48–72 h after the last hMG injection had a lower fertilization rate and an increased percentage of degenerate oocytes than women who received hCG 24 h after the last hMG injection. Thus even in women with normal hypothalamic pituitary function, the interruption in exogenous gonadotrophic stimulation may lead to impaired oocyte activity in at least some follicles. This may mean that during hMG therapy there is an inhibitory effect due either to the exogenously administered menotrophins or to intrinsic follicular components (inhibin?) on the appropriate action of the hypothalamic-pituitary-ovarian axis (De Jong & Robertson 1985).

The three pregnancies occurred in cycles where plasma E2 levels rose after hMG was withheld. In all three women, a steep increase in oestrogenic activity, unaccompanied by adequate follicular growth (leading follicle ≤10 mm in diameter), prompted the physician to foresee the risks and to stop hMG treatment. It is known that multiple small follicles can contribute significantly to oestrogen secretion, and in some women high oestrogen levels are found in the presence of only multiple small ovarian follicles, <11 mm in diameter (Shalev *et al.* 1984) Further exogenous stimulation in such patients leads to excessive oestrogen levels by the time the follicles reach an adequate size for ovulation Thus, it was decided to include these women in the present study to determine whether an early discontinuation of hMG would change the expected course. In each of the three women the relatively small follicles continued to grow and to reach maturity despite the interruption in exogenous gonadotrophin stimulation. The behaviour of these small follicles contrasted with the course of events seen in patients with larger follicles (11–15 mm in diameter) during the pause between the last hMG injection and the first hCG administration. From our results, it appears that the group of follicles < 11 mm was less affected by the discontinuation of exogenous menotrophins than the group of bigger follicles (>11 mm in diameter).

Little is known about the changing dependence of ovarian follicles on gonadotrophic support in the periovulatory stage in man. In other primates after the 'selection' of a follicle destined to ovulate, the dominant follicle requires continued FSH support throughout the follicular phase and even in the immediate preovulatory interval (diZerega *et al.* 1981). It remains uncertain whether our observations suggest a different course of events in women.

Acknowledgments

We would like to thank Miss Lea Eckstein and Mrs Lea Weinberg for performing the ultrasonic examinations and Mrs Reni Ben-Michael, Mr Dubi Tickozky and Mr Nissim Loya of the endocrine laboratory for their assistance and Mrs Nadia Levy for the graphics.

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Received 19 August 1986
Accepted 28 March 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1103–1104

Pre-eclampsia in a woman with homozygous PiZZ alpha-1 antitrypsin deficiency. Case report

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Case report

A 26-year-old primigravida with homozygous PiZZ alpha-1 antitrypsin deficiency was seen at 14 weeks gestation by certain dates. She did not smoke. The condition was diagnosed at the age of 11 when her brother, then aged 16, died of a ruptured cirrhotic nodule. Her liver biopsy in 1985 showed a normal architecture and several small foci of PAS-positive globules within hepatocytes. Liver function tests were normal then, as they were at booking. Blood pressure at booking was 115/65 mmHg. Her partner's phenotype was PiMM.

She was seen regularly from 23 weeks gestation onwards. Serial ultrasound scans showed the fetus to be small-for-dates with a slight tail-off in growth, but the pregnancy was otherwise unremarkable. She was admitted at 36 weeks with a blood pressure of 140/100 mmHg but without proteinuria. Plasma uric acid was 469 μmol/l. She complained of pruritus but the plasma bilirubin level was normal and plasma aspartate transaminase was slightly elevated at 55 i.u./l. Investigation for possible hepatitis or gall bladder disease was negative. At 37 weeks the blood pressure rose to 160/110 mmHg and she was treated with methyldopa after an initial acute dose of nifedipine. She remained aproteinuric. All measures of fetal well-being were normal, but plasma aspartate transaminase levels rose to 62 i.u./l and so labour was induced with a 5 mg prostaglandin pessary. After an uneventful labour involving pethidine and Entonox analgesia, she had a normal vaginal delivery of a healthy 2536 g girl with Apgar scores of 8 and 10 at 1 and 5 min respectively. Cord blood pH was 7·23 (vein) and 7·21 (artery). Methyldopa was stopped 3 days after delivery and she remained normotensive thereafter. Ten days after delivery she had a postpartum haemorrhage. There was no histological evidence of retained products in the curettings from her uterus. Six weeks after delivery her liver function tests were normal. At no stage were her blood clotting tests abnormal.

Discussion

Human plasma contains three main protease inhibitors with activity against coagulant enzymes: antithrombin III, alpha-2 macroglobulin, and alpha-1 antitrypsin. Antithrombin III is the most important: its deficiency leads to a risk of thromboembolism from unopposed thrombin activity (Thaler & Lechner 1981), which is increased in pregnancy (Hellgren *et al.* 1982). There is no evidence of such a risk in alpha-1 antitrypsin deficiency.

In pregnancy, the increase in factors promoting coagulation is balanced by increased antithrombin activity. Alpha-1 antitrypsin has been shown to play the major role from the second trimester onwards and not antithrombin III (Teisner *et al.* 1982). Women with pre-eclampsia have been found to have low antithrombin III levels, in plasma but not serum, caused by an activation of the clotting system (Armstrong *et al.* 1986; Gow *et al.* 1983; Weenik *et al.* 1983). If pre-eclampsia arises owing to activation of the clotting system with fibrin deposition in the basal and spiral arteries, as has been suggested (McKay *et al.* 1953), then theoretically women with protease inhibitor deficiencies are at increased risk of developing the condition. However, women with inherited antithrombin III deficiency do not appear to be particularly at risk from pre-eclampsia. Whether women with alpha-1 antitrypsin deficiency are at risk may be seen when further pregnancies are studied.

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Alpha-1 antitrypsin deficiency is an autosomal recessive condition. It is associated with emphysematous lung disease (especially in smokers), liver disease often presenting as jaundice in infancy and, rarely, glomerulonephritis (Larsson 1978; Moroz *et al.* 1976). Alpha-1 antitrypsin is a protease inhibitor with a single autosomal locus (Pi) on chromosome 14q (Cox *et al.* 1982) and 30 identified co-dominant alleles The phenotype determines the level of circulating alpha-1 antitrypsin, PiMM being the normal. In the homozygous state, PiZZ, alpha-1 antitrypsin and the alpha-1 globulin band on serum electrophoresis, are absent; in heterozygotes (PiMZ) levels may be as low as 60%.

Antenatal diagnosis is important for women with a child already affected by liver disease; 6% of homozygous children develop severe liver disease but if one child is affected the prognosis for subsequent homozygous siblings may be worse than average (Sveger & Thelin 1981).

The antenatal diagnosis of fetal alpha-1 antitrypsin deficiency, although of no relevance in this case because of the father's normal genotype, is possible. Until recently fetal blood needed to be sampled because amniotic fluid cells cannot be cultured (Jeppsson *et al.* 1981). The diagnosis can now be made with chorionic villus biopsy in the second trimester (Gustavii *et al.* 1986). Immunoperoxidase studies and electron microscopy have shown that the condition affects the fetal liver in a 20-week aborted fetus (Roberts 1985).

The incidence of homozygous alpha-1 antitrypsin deficiency in the UK is 1:3400; its prognosis is poor and it is therefore not surprising to find only one other report of pregnancy in a homozygous woman, which was complicated by severe obstructive airways disease (Giesler *et al.* 1977).

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Received 3 November 1986
Accepted 12 February 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1105–1106

Klippel–Trenaunay syndrome—a rare cause of severe menorrhagia. Case report

A. R. MARKOS

Case report

A 26-year-old woman attended the gynaecological clinic with a history of very heavy periods since her menarche in 1971 at the age of 12. She also had gigantism of the right lower limb and angiography had demonstrated multiple arteriovenous malformations at the level of the knee and hip. A 'stapling operation' had been undertaken previously in an attempt to correct the knee abnormality.

Her first menstrual period was heavy and necessitated emergency admission and blood transfusion. She was investigated by examination under anaesthesia and dilatation and curettage which were unremarkable. Treatment with oral ethamsylate (Dicynene), 500 mg four times daily, was given and continued for 3 months during which there was no noticeable change in blood loss. Blood transfusion was required on 12 occasions over the next few years and the maximum volume transfused during the course of any one protracted period was 40 units.

In 1978 treatment was changed to norethisterone, 10 mg daily, from days 5–25 of the cycle. This resulted in a significant decrease in the blood loss, she did not require further blood transfusions, and the haemoglobin concentration remained within normal limits. After 15 months on this regimen, treatment was changed to levonorgestrel, one 250 µg tablet daily, continuously for 3 months followed by 1 week without medication, during which time she had an acceptable withdrawal bleed.

In 1982 retrograde aortic angiography (Fig. 1) was performed and demonstrated uterine arterio-venous malformation (haemangioma). During the same period a skin biopsy was taken in the course of investigations for eczema. This reported 'dermal capillary hyperplasia, in association with extravasation of red blood cells and prominent haemosiderin pigment deposition in the stroma'.

This appearance is consistent with pseudo Kaposi's sarcoma of Klippel–Trenaunay syndrome. The patient was referred to a vascular surgeon who considered that embolization was not advisable for the following reasons: accidental embolization of the superior vesical artery was a possibility; the lesion would continue to be supplied by the vessels from the contralateral side if only one side was embolized, and extensive visceral necrosis was likely if both sides were embolized.

The patient was advised against pregnancy and is seeking to adopt a child.

Discussion

Persistence of the sciatic venous system in various forms gives rise to a large group of venous anomalies in the limb under the general title of 'Klippel–Trenaunay syndrome' (Klippel & Trenaunay 1900). All forms have two features in common: they are congenital, and while they predominantly affect the lower limb, the general vascular territory of the internal iliac vein and artery are also frequently involved.

There are three main clinical degrees:

Type I. The fully developed picture with marked skin angiomas and angiomatous abnormalities consisting of many small and large venous and lymphatic spaces affecting muscles, bones and the internal iliac vein. There may also be arteriovenous fistulae leading to localized gigantism The vascular abnormality may rarely extend through all the tissues of the pelvis. It is advis-

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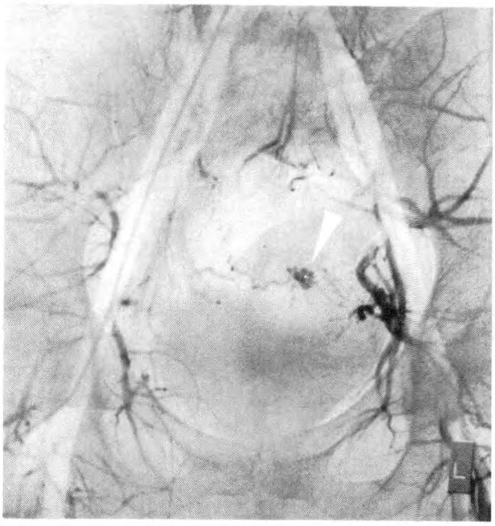

Fig. 1. Retrograde arteriogram. Arterio-venous haemangioma of the internal iliac artery.

able to leave these cases as surgery may prove catastrophic (Dodd & Cockett 1976).

Type II. There is no arterio-venous fistulae but diffuse cavernous haemangiomata.

Type III. A minor form with diffuse varicose veins. Very severe menorrhagia resulting from uterine haemangiomata is uncommon (Lu-Tao-p-ei *et al.* 1973). Pregnancy may occur rarely and spontaneous uterine rupture has been reported (Dawood *et al.* 1972). Ethamsylate was more successful than hormonal therapy in controlling the bleeding in one woman (Milton & Thonet 1981) who had an uneventful pregnancy and was treated by postpartum hysterectomy.

Our patient has the fully blown picture of Klippel–Trenaunay syndrome (type I). As embolization and surgical intervention are unacceptable, hormonal treatment was tried and successfully controlled the bleeding. She was advised against pregnancy because of the possibility of spontaneous uterine rupture and the possible need for surgery.

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Received 5 January 1987
Accepted 14 April 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1107–1110

Removal of a giant ovarian cyst with an uneventful recovery. Case report

OLIVER M. FENTON

Case report

The patient was a 69-year-old widow who lived with her son and daughter-in-law. She was admitted to St Albans City Hospital in February 1980 by the combined efforts of six men from the Ambulance and Fire Services. On admission, she admitted that for the past 5 years, her abdomen had slowly enlarged and now she was having extreme difficulty in getting about. She had resisted all previous attempts by her family to get her into hospital because of fear of the medical profession. Apart from her forced immobility, she had no other complaints and said that she was in good health. She had never been in hospital before and had no other relevant medical history.

She was a very pleasant, talkative lady in no apparent distress. Her overall appearance was that of a very thin woman attached to an enormous mass protruding from her abdomen (Fig. 1). The skin over this mass was coarse and was marked by the passage of enormous superficial veins. There was some evidence of pressure necrosis of the skin on one side of the abdomen, compatible with long periods of immobility. Her cardiovascular and respiratory systems were normal. Investigations showed her urea and electrolytes, haemoglobin, white cell count and blood glucose to be within normal limits. Her alkaline phosphatase was slightly high at 373 i.u./l which was attributed to her immobility. The rest of her liver function tests were normal. X-rays were not possible because she was only able to lie on her side and portable films were therefore difficult.

She agreed, slightly reluctantly, to the removal of the ovarian cyst. With great difficulty, her pre-operative weight was measured in a weighing chair at just over 127 kg (20 stone). In the operating theatre she was placed in a right lateral position on the operating table with an adjacent dressing trolley used to take the weight of her abdomen which protruded over the edge of the table. Anaesthesia was induced in this position using intravenous ketamine and pancuronium. She was subsequently maintained on fentanyl, droperidol and gas-oxygen, on intermittent positive pressure ventilation. After standard skin preparation, a small incision was made in the midline of the abdomen through skin and cyst, and two large suckers, connected to independent suction apparatus, were promptly inserted. Two teams changed the rapidly filling suction apparatus bottles. Seventy-five litres of straw-coloured fluid were removed in this fashion and a further few litres were lost on towels and gowns. The time taken to remove this fluid was approximately 15 min. During this period, her blood pressure varied from 130/100 to 100/80 mmHg. Her pulse was steady at between 90 and 100 beats/min. There were no problems with ventilation. The skin wound was then lengthened in the midline and a right ovarian cyst was removed. The cyst wall was adherent to the parietal peritoneum in some parts of the anterior abdominal wall, but, in general, it was simple to remove and it was of interest that the other abdominal viscera seemed remarkably undisturbed by its presence, showing no signs of compression or displacement. There was also a small cyst on the left ovary which was excised. There remained the problem of the mass of redundant abdominal skin. It was decided to leave this intact as it was felt that excision would result in the removal of most of her, admittedly attenuated, abdominal muscles. We were further put off by the size of the surface veins. Therefore, after closure of her abdominal wound, without drainage, the redundant skin was folded back into the abdomen and a pressure dressing was applied using a large pillow

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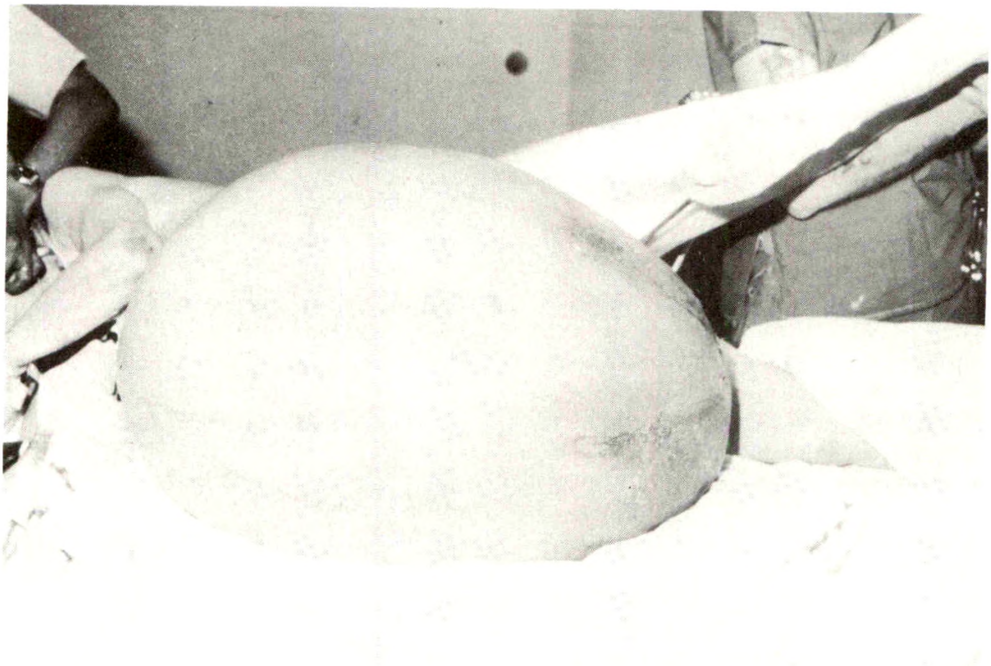

Fig. 1. Pre-operative view of a patient with giant ovarian cyst. Note large veins on abdomen and complete absence of lower limb oedema or lower rib flaring.

held in place with crepe bandages to keep the skin within the confines of the abdominal cavity.

Postoperative recovery was completely uneventful and her initial comments the following day were that she was feeling very well and very much lighter. She was up and about on the third postoperative day, her pressure dressing was removed at 1 week and sutures were removed on the day of discharge, 14 days after operation. She was left with only a slight skin apron remaining from her redundant abdominal skin (Fig. 2), which was controlled with an abdominal support.

In the first postoperative week, her total protein fell to 49 g/l with an albumin of 27 g/l but these had both returned to normal by the time of her discharge.

The histology of the cyst showed it to be a benign pseudomucinous cyst of the ovary. Her weight when she left hospital was 47·6 kg, making the weight of the ovarian cyst 79·4 kg (12·5 stone).

When seen in the outpatients department 2 months later, the lax abdominal skin had contracted in a remarkable fashion, leaving her with little more than a pot belly of extremely coarse skin, which she insisted was well controlled with the abdominal support, and she refused any suggestion of further surgery.

Discussion

This case represents the largest ovarian cyst recorded in this country this century, and the largest ever removed in this country with survival (Drife & Trotter 1981). More remarkable was the complete lack of operative and postoperative complications, which usually attend the removal of a cyst of this size.

In their book on pelvic neoplasms, Lynch & Maxwell (1922) record the world's largest ovarian cysts in descending order. The largest ever reported was from Texas in 1905 and weighed 169 kg; the largest reported in this country is that of Martineau which weighed 98 kg (Lynch & Maxwell 1922). As pointed out in the chapter on 'Mammoth Ovarian Tumours' (Lynch & Maxwell 1922), there are certain discrepancies inherent in measuring cysts of this size. In many of the cases, the fluid was tapped from the tumour before operation, and the weight of fluid that was tapped was then added to the weight of the cyst after its removal to give the overall weight of the cyst, but these tappings were commonly repeated for many days before

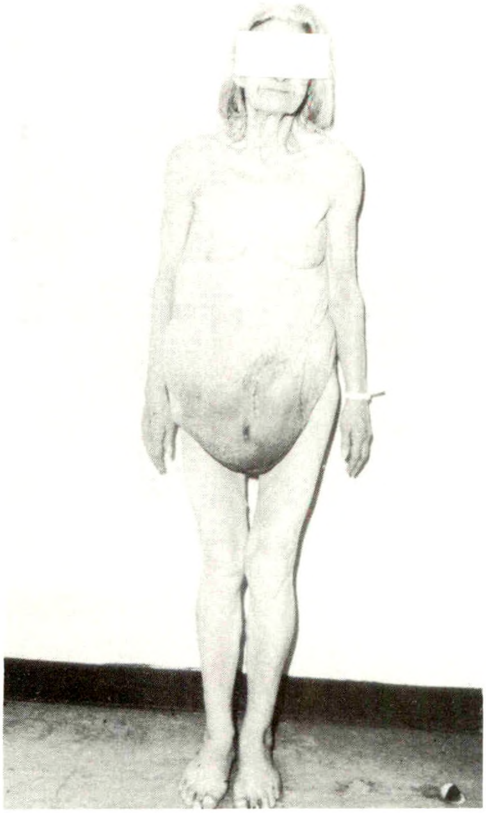

Fig. 2. Two weeks postoperatively. The skin has already contracted.

the final operation which would presumably allow some fluid to reaccumulate. The other main method used is to determine the patient's weight before and after operation. Unfortunately, as in our case, it is not always possible to weigh the patient immediately after an operation and this may give rise to some inaccuracy in the final result, but compared to the great weight of the cyst, this is probably not of major importance.

The removal of massive ovarian cysts is associated with quite a high mortality and morbidity, which is in marked contrast to our case (Lynch & Maxwell 1922; Hunter 1980; Symmonds *et al.* 1963). In the series reported by Lynch & Maxwell (1922) there was a 29% operative mortality. This figure has been improved in more modern times, but a stormy postoperative course is usual. In looking for reasons as to why our case was so trouble-free, several points arise. The first, and probably most important, was the exophytic nature of the cyst. The patient had the appearance of a thin woman attached at one point to a massive abdominal swelling. There was a complete absence of lower limb oedema and flaring of the rib cage, and at operation the other abdominal contents showed little displacement. This is in contrast to other cases where a photograph or accurate description is available (Symmonds *et al.* 1963; Drife & Trotter 1981). Her general condition pre-operatively is another indication of how well her body had come to terms with her cyst. The second factor was the decision to remove the cyst and contents at a single operation. In the past, many of these tumours have been removed in stages, fluid first being removed by paracentesis, followed by a second operation for the removal of the cyst itself. This was presumably done on the grounds that the subsequent operation would be much easier, and that the slow release of such pressure in the abdomen would allow the cardiovascular and respiratory system to return to normal before the final operation. Some patients have been managed by frequent tappings alone and Lynch & Maxwell (1922) reported a woman who, over a 42-year period, had 17 000 pints of fluid removed in this fashion. Unfortunately, such tappings are not without complications and several patients are reported to have died of infection or exhaustion from this course, and the risks of seeding an ovarian carcinoma are probably high. These points have been stressed by other authors (Hunter 1980; Symmonds *et al.* 1963). In our patient, rapid release of the fluid with the patient in a lateral position did not appear to have any deleterious effects on her cardiovascular or respiratory systems, either during or after the operation. Also, if we had undertaken a staged procedure, it is likely that our second operation would have occurred at a time when the patient's plasma proteins had dropped to below normal levels, which might, in association with a second anaesthetic, have impaired her ability to recover satisfactorily. Thirdly, it seems that excision of vast quantities of anterior abdominal wall is unnecessary and is likely to increase the morbidity of this procedure. Lynch & Maxwell (1922) stated that in most of the cases they reviewed, the abdominal wall was left intact and that there was no mention of problems with visceroptosis. It seems that it is possible to rely on the remarkable properties of the skin and soft tissues to restore the patient's contour to the same shape as that which might be achieved by surgery. Finally, the application of an abdominal pressure dressing in the form of a pillow for the first postoperative week may well have reduced possible problems associated with a sudden reduction in intra-abdominal pressure and abdominal contents prolapsing into a large redundant abdominal cavity (Symmonds *et al.* 1963).

Acknowledgments

I would like to thank Sir Reginald Murley, KBE, PPRCS and Professor Harold Rodgers, FRCS, for allowing me to report on this patient under their care; also the Medical Illustration Department at St Thomas' Hospital for the photographs.

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Received 2 February 1985
Resubmitted 25 February 1987
Accepted 2 March 1987

British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1111–1112

SHORT COMMUNICATIONS

Maternal serum alpha-fetoprotein and ethnic origin

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Shapiro and his colleagues have reported that the mean maternal serum alpha-fetoprotein (MS-AFP) level in 24 women of Asian origin was only 57% of that in a similar number of Caucasian women, a statistically significant reduction (Shapiro *et al.* 1975). In view of the potential importance of this observation in the interpretation of MS-AFP screening test results for neural tube defects and Down's syndrome, we decided to investigate the matter further.

Methods and results

During the period 1972–1983, about 30 000 women who booked for their antenatal care at the John Radcliffe Maternity Hospital, Oxford, had MS-AFP tests. We reviewed the family names of these women and classified them as 'Asian' (i.e. originating from the Indian subcontinent), a method which has been shown to be specific and sensitive (Nicoll *et al.* 1986). A list of names compiled by the Office of Population Censuses and Surveys and another by Bradford Metropolitan District Community Relations Council were used as guides to the classification. Although the family names could be from women of Arabic origin or from non-Asian women married to Asians, this was thought to be very much the exception in Oxford during the period concerned (Oxford Council for Community Relations, personal communication).

MS-AFP levels were expressed in multiples of the median value (MoM) for the appropriate gestational age. Gestation was based on the time since the first day of the last menstrual period. Multiple pregnancies and those affected by fetal neural-tube defect or Down's syndrome were excluded from the analysis.

Table 1 shows that the median MS-AFP level in Asians was 94% of the value in non-Asians; a small but nonetheless statistically significant difference ($P<0\cdot02$, Mann–Whitney *U*-test), confirming the observation by Shapiro *et al.* (1975). The reduction is probably too small to justify any adjustment when interpreting MS-AFP results in Asian women. In support of this view the proportion of women with raised MS-AFP levels ($\geq 2\cdot5$ MoM) was only slightly less in Asian women than in non-Asian women, 2·4% (13/531) compared with 2·6% (700/26 818), and the proportion with low MS-AFP levels ($<0\cdot5$ MoM) was also similar, 10·4% (55/531) compared with 9·0% (2416/26 818).

The reduced MS-AFP levels in women of Asian origin was not explained by increased maternal weight. A subset of data included both maternal weight and MS-AFP and for this subset of MS-AFP results we adjusted for maternal weight as described previously (Wald *et al.* 1981); the MS-AFP difference persisted (medians of 0·93 MoM in 80 Asians and 1·00 MoM in 4231 non-Asians; $P=0\cdot12$, Mann–Whitney *U*-test). The reduced MS-AFP levels were also not explained by any tendency for gestational age to be overestimated in Asian women. This was assessed using another subset of data that included biparietal diameter measurements done routinely as part of a randomized trial of

Table 1. Maternal serum alpha-fetoprotein (AFP) levels according to ethnic origin

Centile	Maternal serum AFP (MoM)	
	Asians	Non-Asians
25th	0·68	0·73
50th (median)	0·94*	1·00*
75th	1·30	1·35
No. tested	531	26 818

* Difference statistically significant, $P<0\cdot02$, Mann–Whitney *U*-test.

ultrasound (Wald *et al.* 1982). Adjusting the MoM AFP value after estimating gestational age using this measurement again did not abolish the difference (medians of 0·86 MoM in 34 Asians, and 1·00 MoM in 2077 non-Asians; $P = 0{\cdot}06$, Mann–Whitney *U*-test). It is possible that the reduced MS-AFP levels in Asian women are due to diminished fetal production since the median amniotic fluid AFP level was also low in 143 Asian women tested in Oxford in 1973–1984 (0·96 MoM) and the source of both maternal serum and amniotic fluid AFP is the fetal liver.

Discussion

These MS-AFP differences between Asian and non-Asian women are not the only examples of ethnic differences in AFP levels. MS-AFP levels in American blacks have been shown to be higher than in non-blacks in three studies (Crandall *et al.* 1983; Johnson 1985; Baumgarten 1986) based on a total of 3508 blacks and 45 774 non-blacks. A fourth study (Macri *et al.* 1976) based on 46 blacks and 59 non-blacks did not find such an effect. A study in men showed that serum AFP levels in residents of Kenya and the Ivory Coast were higher than in residents of Singapore and France (Sizaret *et al.* 1975). The explanation for these ethnic differences in AFP levels is not known.

Acknowledgments

We thank Swaran Chandi and Rajalakshm Gangadharam for helping to classify names, Mr L. Bulusu and Miss G. Kaur-Sadhu of the Office of Population Censuses and Surveys who supplied a list of Asian names, the Oxford Council for Community Relations who provided advice on the extent to which the names we used would identify Asians, and Mr B. Solanki of Aylesbury Vale Council for Racial Equality for supplying an additional list of Asian names.

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Received 16 April 1987
Accepted 30 April 1987

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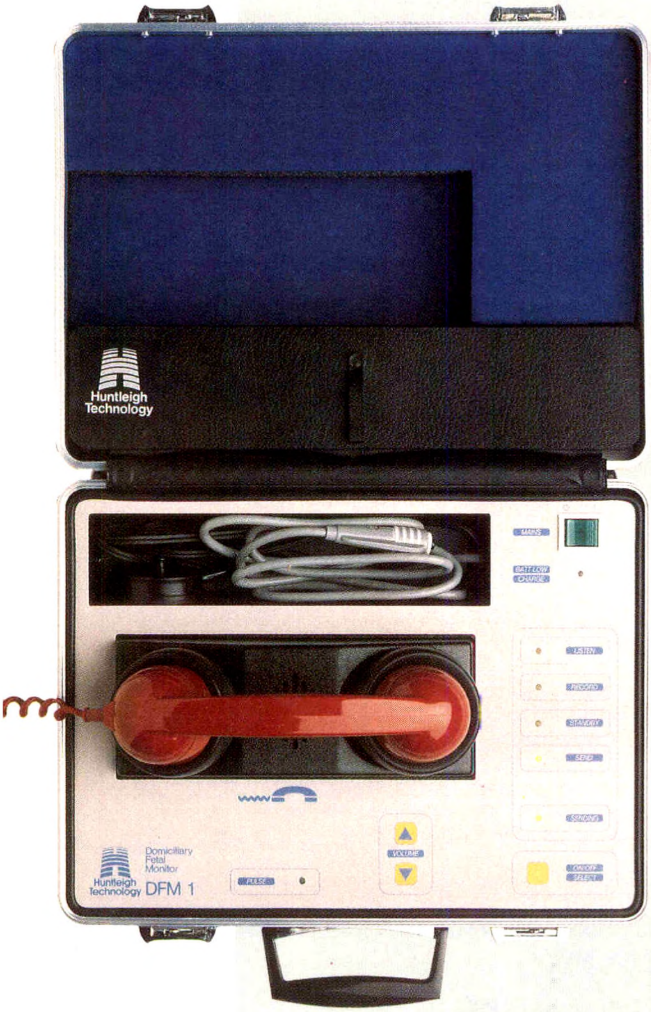

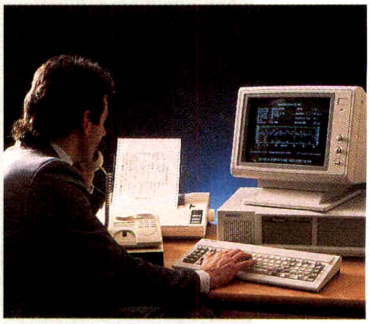

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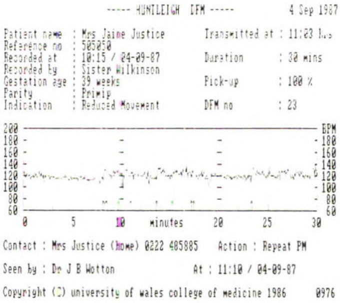

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        ----- HUNTLEIGH  DFM -----          4 Sep 1987

Patient name   : Mrs Jaime Justice       Transmitted at : 11:23 hrs
Reference no   : 505050
Recorded at    : 10:15 / 04-09-87        Duration       : 30 mins
Recorded by    : Sister Wilkinson
Gestation age  : 39 weeks                Pick-up        : 100 %
Parity         : Primip
Indication     : Reduced Movement        DFM no         : 23

200 ----------------------------------------------- BPM
180 -                                              - 180
160 -                                              - 160
140 -                                              - 140
120 -                                              - 120
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 80 -                                              -  80
 60 -----------------------------------------------   60
    0       5       10    minutes    20       25      30

Contact : Mrs Justice (home) 0222 405885    Action : Repeat PM

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British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1113–1118

CORRESPONDENCE

Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational-age infants

Dear Sir,

Khong *et al.*[*Br J Obstet Gynaecol* (1986) **93,** 1049–1059] report studies on placentas of pregnancies complicated by pre-eclampsia or small-for-gestational-age (SGA) infants or both. They described an absence of physiological changes in the entire length of some spiral arteries in half the patients. This finding clearly indicates that the spiral arteries had not been colonized by trophoblast at any stage of gestation. They found spiral arteries unaffected by physiological changes in the basal plate of 20 placentas from abnormal pregnancies. In 14 of these 20 placentas both uteroplacental and unaltered spiral arteries were observed in different sections of the basal plate and six had only spiral arteries not showing physiological changes. They did not find absence of physiological changes in the basal plate from normal pregnancies.

Absence of trophoblastic invasion and acute atherosis have been described in spiral arteries of the decidual portion of the placental bed in pregnancies associated with SGA infants without maternal hypertension (de Wolf *et al.* 1980) and also in the spiral arteries of the basal plate of one patient with mild hypertension and circulating serum maternal lupus anticoagulant who gave birth to a macerated SGA fetus (de Wolf *et al.* 1982).

Althabe *et al.* (1985) and Labarrere & Althabe (1985) reported the absence of physiological changes (Fig. 1) and acute atherosis (Fig. 2) in *spiral arteries* of the basal plate, intermingled with vessels showing normal physiological changes, in pre-eclamptic pregnancies with or without SGA infants and in those having idiopathic SGA infants. Only one woman in the normotensive control group, who gave birth to an infant with normal birthweight, showed an absence of trophoblastic invasion in the basal plate (Labarrere & Althabe 1985). Findings of absence of physiological changes in the basal plate were similar to those described by Khong *et al.* (1986). It would be very interesting to know if Khong *et al.* (1986) found acute atherosis-like lesions in the basal plate associated with absence of physiological changes in their revised material, since Robertson *et al.* (1975) and de Wolf *et al.* (1975) have maintained that acute atherosis occurs only in arteries with muscular walls and hence is seen only in spiral arteries in which physiological changes have not taken place.

Khong *et al.* (1986) suggested that pre-eclampsia and SGA without pre-eclampsia were

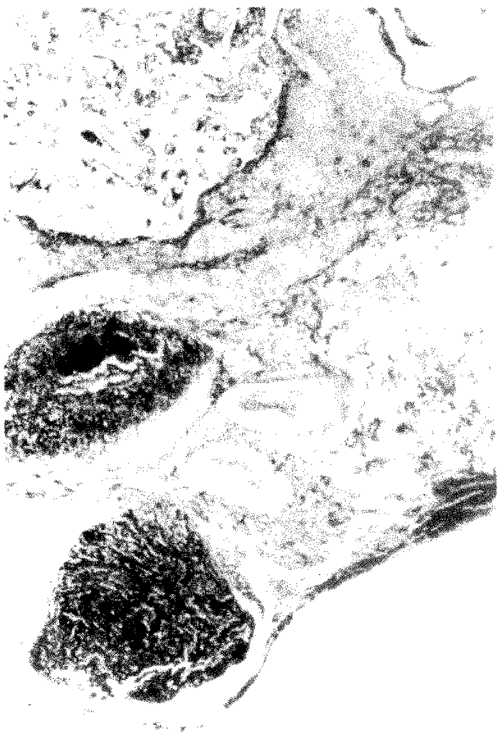

Fig. 1. Spiral artery in the basal plate of a placenta from a small-for-gestational-age infant of unknown aetiology. No physiological changes and preservation of its musculoelastic structure can be seen. Masson's trichrome ×50. This photograph is a low power view of Fig. 2 taken from Althabe *et al.* (1985) and is strikingly similar to Fig. 7 published by Khong *et al.* (1986).

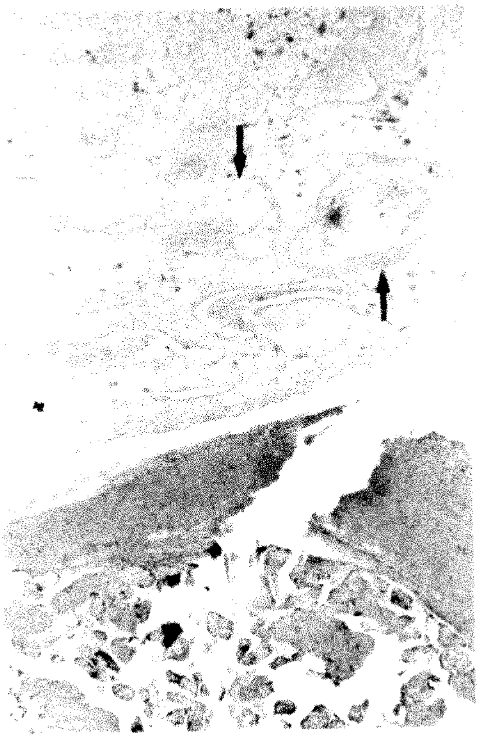

Fig. 2. Spiral arteries of the basal plate in a pre-eclamptic pregnancy with intrauterine growth retardation showing acute atherosis (arrows). Haematoxylin and eosin ×50. The artery on the right is a low power view of Fig. 4 taken from Labarrere & Althabe (1985).

'characterized by a defective interaction of migratory trophoblast with uterine tissues in the establishment and proper development of haemochorial placentation. It is perfectly possible that different aetiological factors can act to produce the same morphological pattern of defective placentation and, while the hypertensive disorders of pregnancy and SGA frequently coexist, it does not necessarily mean that they share aetiological factors'. Interestingly, they maintained that 'the maternal vascular response to placentation in abnormal pregnancies may be inadequate both qualitatively, as shown by the restriction of physiological changes, as well as quantitatively, as shown by the reduction in the number of uteroplacental arteries actually formed'.

Gerretsen *et al.* (1981) proposed that 'the hypertension of pregnancy may be a compensatory mechanism to ensure an adequate blood supply to the placenta when the physiological changes fail to occur and then may exert a favourable influence on the development of the fetus. When this compensatory mechanism is either insufficient or does not appear, the inadequate blood supply will be related to a fetal growth retardation of variable severity'.

Finally, Labarrere & Althabe (1985) suggested that 'the fact that the same lesions were observed in pre-eclampsia with or without intrauterine growth-retarded infants and in idiopathic intrauterine growth retardation may be explained by a similar pathogenesis for both entities. From the above mentioned it seems reasonable to postulate the possibility of a pathophysiological continuum between intrauterine growth retardation of unknown aetiology and pre-eclampsia, where the expression of either hypertension or low birthweight or both may be due to variable maternal reactivity to the fetal implant and to the extension and severity of the placental lesions. This may explain why there is pregnancy-induced hypertension with or without fetal growth retardation and small-for-gestational-age infants without maternal hypertension; all of them with the same placental lesions'.

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Authors' reply

Dear Sir,

We are grateful for the opportunity to reply to the letter by Labarrere & Althabe which summarizes some of the findings presented in our article (Khong *et al.* 1986). We are pleased to note that they have changed their published view (Althabe *et al.* 1985) when 'it has to be stressed, of course, that although absence of physiological changes and acute atherosis were found in the decidua basalis we cannot be certain that these vessels were spiral arteries' to one where they now feel certain that they are spiral arteries.

Our article was concerned with the microanatomy of the blood supply to the placenta in pre-eclampsia and in SGA infants and we deliberately refrained from mentioning vasculopathies which are the subject of a further communication. Suffice it to say that these lesions were seen in the basal plate. The previous argument (Robertson *et al.* 1975) that decidual segments of the uteroplacental arteries in the placental bed, having undergone physiological changes, are relatively immune from acute atherosis and the apparently contradicting findings of acute atherosis in decidual segments (Hertig 1945; Sexton *et al.* 1950; Zeek & Assali 1950; Kitzmiller & Benirschke 1973; Kitzmiller *et al.* 1981; Sheppard & Bonnar 1976, 1981; Hustin *et al.* 1983) can now be explained. The new finding of unaltered spiral arteries throughout their course from their origin from the radial arteries to the openings in the intervillous space will reconcile the opposing views. Such arteries, retaining their musculoelastic tissue, are as prone to acute atherosis as analogous arteries in the decidua vera and myometrium.

Finally, of course, Labarrere & Althabe (1985) are not the first to suggest that pre-eclampsia with or without intrauterine growth-retarded infants and idiopathic intrauterine growth retardation are a continuum. This was suggested by Redman *et al.* (1984) and we ourselves suggested that in these disorders of pregnancy the interaction between fetal and maternal tissues during the establishment and development of placentation may be critical (Robertson *et al.* 1985).

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Growth retardation and fetal hydrocephalus developing after discontinuation of a mid-trimester termination procedure. Case report

Dear Sir,

The case report by Wood *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 372–374] describing growth retardation and fetal hydrocephalus developing after discontinuation of a mid-trimester termination procedure involving intravenous administration of prostaglandin (PG) E_2 prompts us to report the absence of any apparent harm after 'failed' intra-amniotic PGE_2 termination.

In December 1983 a 23-year-old mother of two children, with a history of depression and parasuicide by self-poisoning with clobazam, requested abortion at 18 weeks gestation. Termination of pregnancy was agreed in terms of The Abortion Act (1967) and informed consent to the procedures involved was obtained after thorough counselling. PGE_2, 10 mg diluted in 5 ml 0·9 N NaCl solution, was injected into the amniotic fluid. During the next 24 h she experienced numerous painful uterine contractions but there was no vaginal bleeding and the cervix remained closed. She understood that an intravenous oxytocin infusion was to be given if abortion did not occur within 24 h, but after being visited by her consort she refused further treatment and discharged herself from hospital contrary to medical advice. The pregnancy continued with little medical supervision because she failed to keep appointments. In May 1984, at 41 weeks gestation, she was delivered normally of a male infant, birthweight 3·300 kg. Apgar scores were 7 and 9 after 1 and 10 min respectively and there was no evidence of hydrocephalus (head circumference 36.5 cm), limb deformities, or any other congenital abnormality.

A recent detailed clinical assessment by F.N.P. has confirmed that, at 3 years of age, the child is healthy with normal weight, height and head circumference measurements; there is no evidence of any nervous system or cardiovascular system abnormality and developmental and behavioural assessments were normal.

A distorted impression of risk will emerge if cases of 'failed' abortion with PG are only reported when the fetus is abnormal and Wood *et al.* (1987) recognize that intrauterine viral infection was not completely excluded in their patient. They cite Collins & Mahoney (1983) who described abnormal digits and hydrocephalus after an attempted abortion with vaginal PG in the first trimester but they do not mention the report by Cunanan *et al.* (1977) of a normal, healthy infant born at term after attempts to abort the pregnancy at 15–18 weeks with two intra-amniotic injections of 40 mg $PGF_{2\alpha}$ and an intravenous infusion of oxytocin.

We agree that the fullest counselling should be given before termination but can we legitimately show reluctance to discontinue an abortion procedure in response to such a patient's request? What we need is a reasonably accurate indication of the nature and magnitude of risk which can only be gleaned from precedents.

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Authors' reply

Dear Sir,

We state quite clearly that it is unlikely that an association between prostaglandin (PG) E_2 and oxytocin and congenital malformations in man will ever be established. It is nevertheless true that such a combination given in early pregnancy could constitute an intrauterine insult. It is unreasonable to expect that all patients exposed to a known insult will suffer as a result of that episode and this is the value of case reports when the circumstances are unusual. It is desirable that the decision to begin a termination of pregnancy be absolute; in this regard we have endeavoured to show the possible risk of discontinuing an abortion procedure when the nature and magnitude of that risk is unknown. The fact remains that the ultimate decision is made by the patient but only after a full explanation of the matter including the possibility of anoxic damage to the fetus as dealt with in our case report.

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Plasma renin activity and cAMP in termination of pregnancy induced by sulprostone

Dear Sir,

We were interested and surprised to read the report by Saarikoski *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 328–332] suggesting a pronounced fall in plasma renin activity (PRA) during the intravenous infusion of sulprostone (a derivative of prostaglandin E_2) in the late first trimester pregnancy. We recently published data (Broughton Pipkin *et al.* 1984) from 20 women in early second trimester pregnancy showing the infusion of dinoprostone (a different derivative of prostaglandin E_2) to be associated with a significant increase in plasma renin concentration (PRC) and no change in plasma renin substrate. The data are qualitatively similar to those previously reported in non-pregnant subjects, whereas those of Saarikosi *et al.* (1987) differ markedly, as the authors themselves comment.

Sulprostone (Schering) is a 16-phenoxy derivative of methylsulphonylamide prostaglandin E_2 while dinoprostone (Upjohn) is 11, 15-dehydroxy-9-oxo-prosta-5, 13-dine-l-oic acid. The structural difference might account for the difference in response but a mechanism is not clear. More likely is a change in response with gestational age. Dr. Saarikoski's patients had a mean gestational age of 10·3 weeks (range 7–15) whereas ours were at a mean of 15·6 weeks (range 14–17). Placental steroid and polypeptide hormone production has undergone a substantial increase during this 5-week period, and the production of renin by the fetal membranes in tissue culture is considerable by the end of the period. The difference between the two data sets may identify a time at which the feto-placental renin-angiotensin system begins to influence the maternal system.

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The effect of the duration of the second stage of labour on the acid-base state of the fetus

Dear Sir,

The paper by Katz *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 425–430] is seriously flawed in that no indication is given about how the diagnosis of 'second stage' was made. It is a common mistake to assume that the second stage of labour begins at the time when full dilatation of the cervix is diagnosed. Full dilatation may in fact have been present for some time before the birth attendant makes the observation. Vaginal examination may be performed to confirm full dilatation in the presence of other external signs but equally full dilatation may be a fortuitous finding when vaginal examination is performed for other reasons. Even when performed to confirm external signs of full dilatation, the time lag between the actual occurrence of full dilatation and its confirmation by vaginal examination will usually be a significant proportion of the total 'duration of the second stage'. The authors neither define the beginning of second stage of labour nor explain how they identified that it had occurred. This basic flaw invalidates any conclusions about the effect of simple prolongation of the second stage of labour on umbilical artery lactate levels unless the second stage of labour should be defined as 'that period during which umbilical artery lactate levels are likely to increase'.

In Table 3, the authors clearly show that where there is no end stage deceleration of the fetal heart, then there is no significant increase in umbilical artery lactate regardless of the stated length of the second stage. This appears to be true for both primiparae and multiparae. In the presence of end stage decelerations, however, it would appear that there is a statistically significant increase in umbilical artery lactate levels with prolongation of the second stage. Because of the difficulty in defining the length of second stage, however, it is probably more true to say that, in the presence of end stage decelerations, umbilical artery lactate level rises with longer periods of end stage deceleration.

The authors observe that the 18 infants in their study with 1-min Apgar scores of <7 had a mean umbilical artery lactate of 3·5 nmol/l. Surely the practical import of this study is to confirm that elevated umbilical artery lactate levels are associated with low Apgar scores at birth and that this may be predicted by monitoring during the second stage of labour for end stage decelerations of the fetal heart.

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Katz, M., Lunenfeld, E., Meizner, I., Bashan, N. & Gross, J. (1987) The effect of the duration of the second stage of labour on the acid-base state of the fetus. *Br J Obstet Gynaecol* **94**, 425-430.

Authors' reply

Dear Sir,

Thank you for giving us the opportunity to respond to Lt Col. Young's remarks. Lt Col. Young is undoubtedly right that the precise assessment of duration of second stage labour is of crucial importance when one studies the metabolic impact of duration of the length of second stage labour on the newborn.

In order to diagnose the true onset of second stage as accurately as possible during the study period, we assessed cervical dilatation at 10-min intervals. Starting from 9 cm dilatation, one has to agree that in the present state of the art, this is the best one can do and it is our strong belief that the timing error of this extent could not have had any great influence on the results and conclusions.

Lt Col. Young's point that this was not outlined in the methods section is well taken, but to state that this 'invalidates any conclusion' seems to us unjustified. The fact that during prolonged second stage labour fetal acid-base homeostasis is disrupted, was observed by many investigators (Dellenbach *et al.* 1981; Suidan & Young 1985; Beard *et al.* 1967). Our contribution was that of lactate measurements in correlation to duration of second stage. Those changes are seen, not only in umbilical artery, but also in umbilical vein samples, with values higher in artery than in vein.

In the presence of severe and prolonged deceleration during the second stage of labour, the metabolic impact of suboptimal gas exchange in the intervillous space is enhanced by disturbances in fetal blood flow and, therefore, it is not surprising that acid-base variables and lactate values are frequently abnormal and the degree of abnormality correlates well with duration of deceleration (Katz *et al.* 1982).

As for the predictable value of monitoring, it is well known that whereas normal tracing is a good predictor of a healthy newborn infant, the value of a pathological one is more questionable. We have all seen babies born with 'frightening' fetal heart rate patterns who had normal umbilical artery pH and did perfectly well.

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British Journal of Obstetrics and Gynaecology
November 1987, Vol. 94, pp. 1119–1120

BOOK REVIEWS

Epilepsies and Reproduction. Vols I and II. (Nord Epilepsy Research and Information Group) edited by J. Beaussart-Defaye, N. Bastin & C. Demarcq, under the direction of M. Beaussart. Grine, Lille, FF77 (post paid)

In these two volumes a French research team present their findings from a long-term study of the consequences of epilepsy on the outcome of pregnancy. In Volume I, 212 pregnancies in a group of 100 couples in which the mother had epilepsy are compared with 183 pregnancies in a group of 100 couples in which the father had epilepsy, whether treated or not. They were randomly selected from a population of 3438 individuals singled out from 12 290 cases previously identified in an epidemiological study of epilepsy in men and women living in the Nord-Pas-de-Calais region of France. Volume II contains an analysis of the follow-up of 295 pregnancies in women with epilepsy in the same region between January 1970 and December 1985 (misprinted as 1980 on the title page). The detailed analysis of wide-ranging aspects highlights the various difficulties and complexities inherent in research into epilepsy and parenthood. Unfortunately this has resulted in subdivisions with such small numbers that no statistical conclusions can be drawn from this study. The main concern is with the potential teratogenic effects of anti-epileptic drugs but it is clear that this must be considered in the overall setting including the aetiology and severity of the parental epilepsy and genetic background of both parents. What does emerge is a link between parental epilepsy and/or the mother taking anti-epileptic drugs and the occurrence of malformations in the infant, but the precise mechanism—like the origin of congenital malformations in general—remains to be elucidated. The quality of the print, particularly of the footnotes, is poor and there are numerous minor errors in the figures and spelling. However, for those interested there is a useful review of the literature and bibliography, and the methodology described will facilitate comparison of the work of other researchers in this field.

Michael Espir

The Safety of Diagnostic Ultrasound (British Journal of Radiology Supplement No. 20) edited by P. N. T. Wells. Royal Institute of Radiology, London, 1987, £6.00 (+£1.00 p+p)

Controversies about the safety of diagnostic ultrasound during pregnancy wax and wane. This report was conceived during 1984 when controversy was at a peak and sees its publication in 1987 when the intensity of debate seems to have returned to baseline levels. A dispassionate review of the subject was needed and this has been provided in a lucid and concise style. The experimental and epidemiological studies are complex and are best considered (as here) by a multidisciplinary panel who highlight the confusion that has resulted from the absence of a systematic series of experiments targeted at agreed goals. The difficulties of measuring energy output from ultrasound equipment is discussed; so are the reports of chromosomal damage and increased rates of sister chromatid exchange from exposure to ultrasound *in vitro* and the subsequent failure of confirmation of these findings by other laboratories. The conclusions of this report are, in line with other reviews, reassuring: that there is no evidence that current practice carries any hazard due to ultrasound, but that the search for untoward bioeffects should continue in an orderly and planned fashion.

Those of us who use diagnostic ultrasound during pregnancy have a responsibility to keep abreast of studies of possible biological effects and the British Institute of Radiology has done us a favour by commissioning this report. They would do us a greater favour still if Professor Wells' panel were to continue to meet to review the expanding and diverse literature to produce regular supplements to the current report.

J. P. Neilson

Teratogen Update: Environmentally Induced Birth Defect Risks edited by John L. Sever & Robert L. Brent. Alan R. Liss, Inc., New York, 1986, 264 pages with figures and tables, £53.00

This is an excellent book which provides up-to-date information not only to investigators who deal most of the time with complex teratological problems but also to clinicians and health professionals who may occasionally have to answer questions about congenital defects. Many of the chapters were rewritten or reproduced from *Teratogen Update* reports which have appeared over the past decade: they include drugs, infections, chemicals, as well as physical, nutritional, or other factors considered teratogenic in man. Moreover, a few medicolegal aspects of teratology are discussed such as the education, or rather miseducation, of physicians, lawyers, and the public on the aetiology of human malformation; the inability to answer unanswerable questions; and last but not least malpractice litigation and the role of the expert witness.

Of course thalidomide embryopathy is reviewed again, but the book also includes a very useful description of the wide spectrum of the phenotypic defects.

The role of polypharmacy (for example that of multiple anti-convulsants for the occurrence of fetal hydantoin effects), as well as the genetic impact are briefly mentioned.

The various chapters dealing with infections in relation to birth defects are clearly and well written.

Radiation teratogenesis—an important subject often scarcely discussed—is extensively documented and very informative.

The book appears particularly valuable not only because it compiles many of the known facts in a useful and concise way but also because it considers many unsolved problems that have to be dealt with in the near future. This book is to be welcomed as a source of information and guide to all who are involved with teratological problems.

Beatrice Krauer

Books received some of which may be reviewed at a later date

Drugs and Pregnancy: Human Teratogenesis and Related Problems Second edition edited by D. F. Hawkins. Churchill Livingstone, Edinburgh, 1987, 349 pages with figures and tables, £17.50

Pregnancy Loss: Medical Therapeutics and Practical Considerations edited by James R. Woods Jr & Jenifer L. Esposito. Williams & Wilkins, Baltimore, 1987, 355 pages, £30.00

Prenatal Ultrasound. A Colour Atlas with Anatomic and Pathologic Correlation by B. A. Spirt, L. P. Gordon & M. Oliphant. Photographs by J. G. Hodgson. Churchill Livingstone, New York, 1987, 147 pages fully illustrated, £49.50

Neonatal and Perinatal Medicine: Diseases of the Fetus and Infant Fourth edition edited by A. A. Fanaroff & R. J. Martin. C. V. Mosby Co., St Louis, 1987, 1232 pages with figures and tables, £75.00

Obstetrics for Students by A. M. Nysenbaum. Churchill Livingstone, Edinburgh, 1987, 221 pages, £5.95

Immunology of the Male Reproductive System (Immunology Series/36) edited by P. E. Bigazzi. Marcel Dekker, Inc., New York, 1987, 418 pages with figures and tables, $110 (USA and Canada), $132 (elsewhere)

A Colour Atlas of Omental Transposition for Advanced Breast Carcinoma (Single Surgical Procedures 42) by Harvey White. Wolfe Medical Publications Ltd, London, 1987, 63 pages with colour plates, £17.00

Eating Disorders—The Facts Second edition by Suzanne Abraham & Derek Llewellyn Jones. Oxford University Press, Oxford, 1987, 162 pages with figures and tables, £4.95 (paperback), £8.95 (hardback)

Giving Birth. How it Really Feels by Sheila Kitzinger. Victor Gollancz Ltd, London, 1987, 224 pages illustrated, £4.95 (paperback), £11.95 (hardback)

Oxford Handbook of Clinical Specialities by J. A. B. Collier & J. M. Longmore. Oxford University Press, Oxford, 1987, 787 pages, £9.95

Watch your Child's Weight by Jennifer Ashcroft & R. Glynn Owens. Oxford University Press, Oxford, 1987, 146 pages, £4.95

Towards Happy Motherhood—Understanding Postnatal Depression by Maggie Comport. Corgi Books—Transworld Publishers Ltd, London, 1987, 329 pages, £4.95

Proceedings and symposia

Highlights on Endocrinology Proceedings of the First European Congress of Endocrinology, 1987, edited by Claus Christiansen & Bente Juel Riis, 436 pages with figures and tables, Danish Kr. 750

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution: major changes will be agreed with the author(s).

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Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used; the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables. The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s).

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Tables and figures
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Authors are referred to the general statistical guidelines of Altman *et al.* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

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Trudinger, B. J., Lewis, P. J. & Petit, B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86**, 432-436.

Hytten, F. E. & Leitch, I. (1971) *The Physiology of Human Pregnancy* 2nd edn. Blackwell Scientific Publications, Oxford, p. 26.

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Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent. Only essential corrections can be accepted; more extensive alterations, which may delay publication, will be charged to the author. Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed card sent with the proofs.

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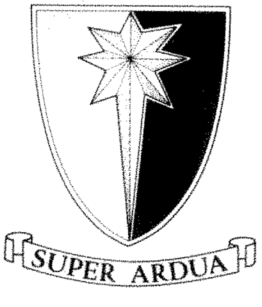
Volume 94, Number 12, December 1987

British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten



Published on behalf of the
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by Blackwell Scientific Publications
BJOGAS 94(12) 1121–1254 1987 ISSN 0306-5456

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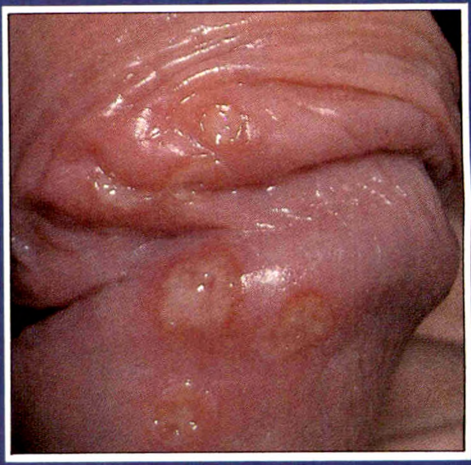

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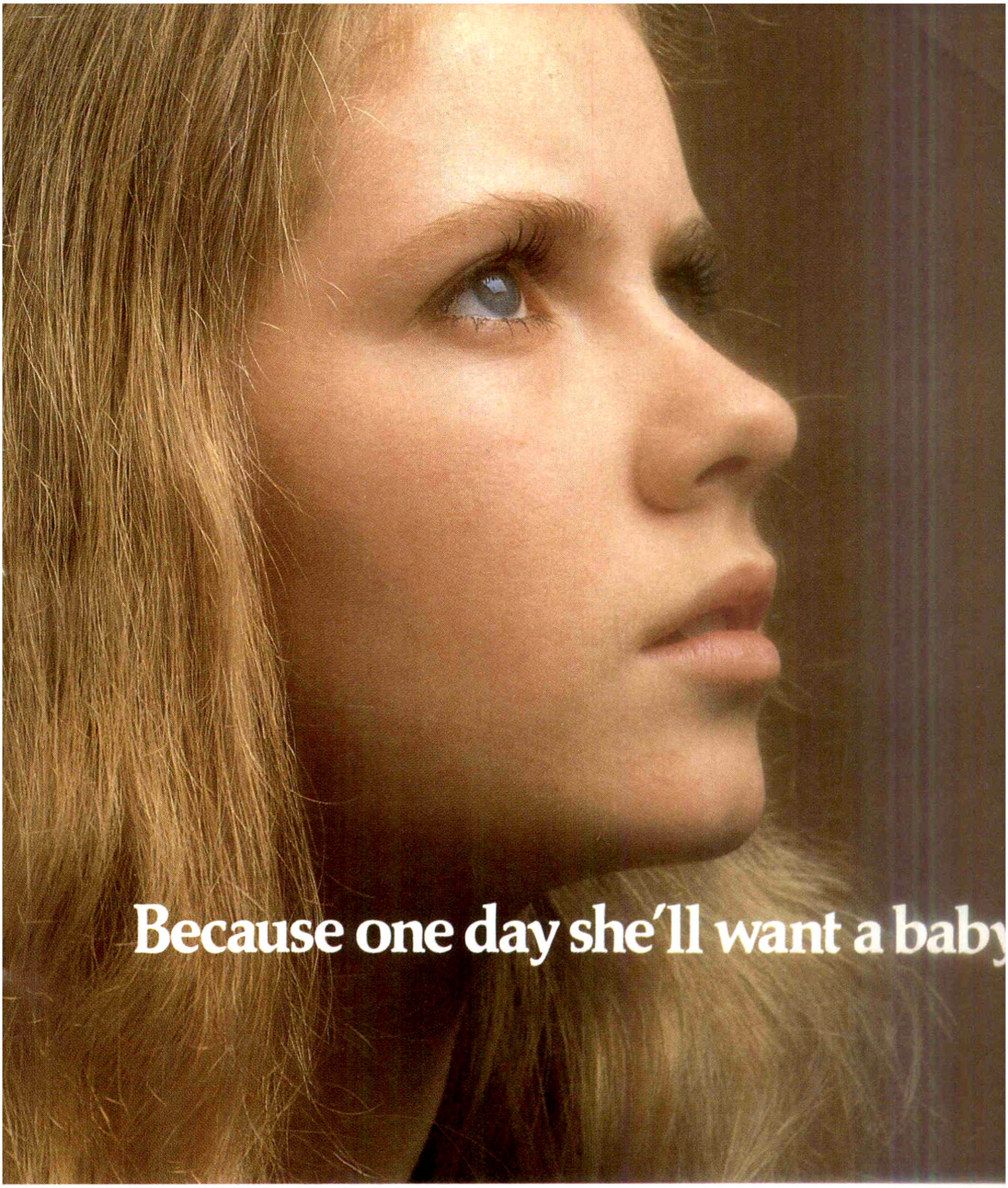
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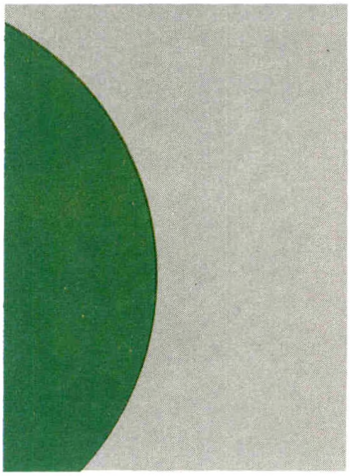

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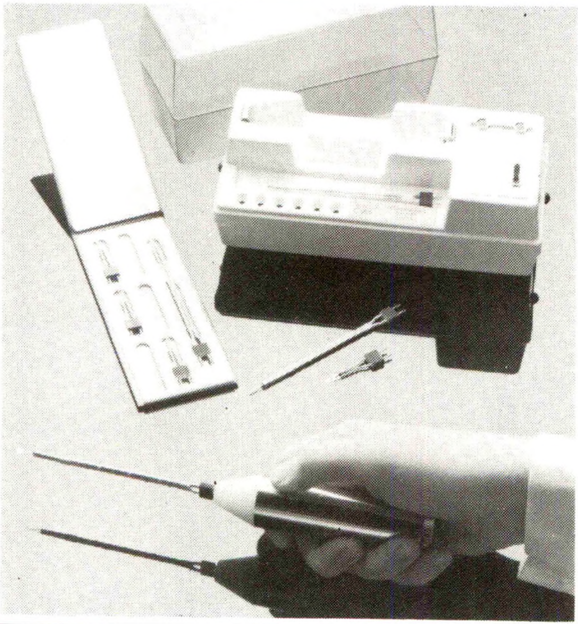

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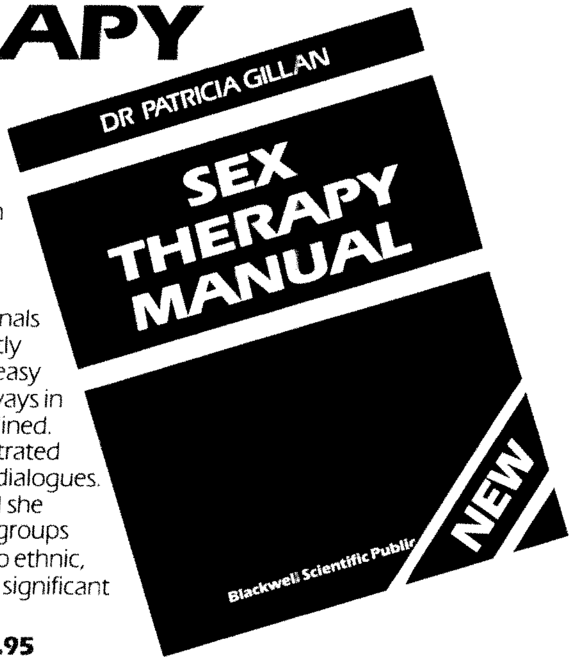

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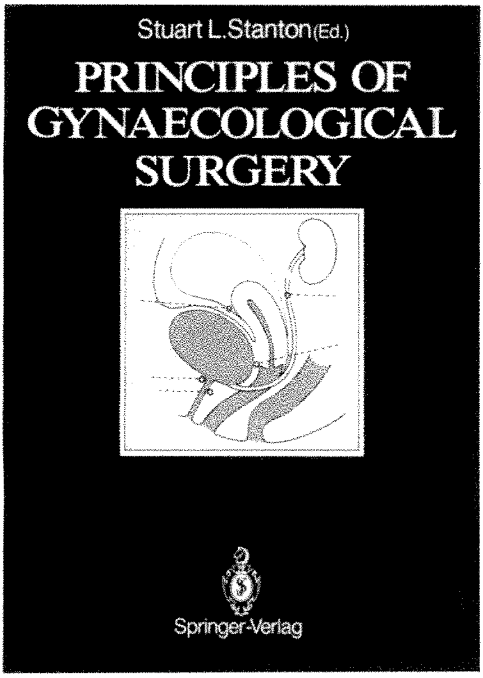

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British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1121–1122

COMMENTARY

The safety of diagnostic ultrasound

Amongst the scientific presentations at the first meeting of the British Medical Ultrasound Group 17 years ago and the first European meeting on ultrasound in Rotterdam in 1973 were several papers concerning the potential effects of ultrasound energy upon biological systems. Macintosh & Davey (1970) published a paper purporting to show chromosome aberrations induced by an ultrasonic fetal pulse detector. Although the authors of this paper subsequently failed to reproduce their results and had to retract their opinion, the whole question of the potential safety of diagnostic ultrasound had been raised, never to be forgotten. The whole subject received a further impetus from the publicity surrounding the publication by Liebeskind *et al.* (1979) in the USA claiming to show sister chromatid exchanges in human lymphocytes after exposure to diagnostic ultrasound. This work has also been subsequently questioned and to date has not been reproduced by an independent laboratory.

Several national and international bodies have subsequently felt it advisable to publish statements on their view of the safety of diagnostic ultrasound and certainly those of repute have all concluded that there is no evidence of any adverse effects on intact human patients, their offspring or the equipment operators by diagnostic ultrasound procedures. But most statements advise caution and emphasize the need for further research.

It is perhaps reassuring that the vast majority of papers published to date have failed to demonstrate adverse effects but one recently published review of these papers (Wells 1987) concludes that the current scientific evidence presents a picture of confusion, that most experiments are unrelated to each other, poorly designed and have no common endpoints in sight. The biological systems examined include insects, plants, cell suspensions and intact small mammals and the relevance of these to intact man must be regarded as extremely questionable. Clearly, however, such experiments are necessary to identify possible mechanisms by which bio-effects might occur and to attempt to predict the sort of effects which might be expected.

Perhaps the most logical starting point in an assessment of the safety of ultrasound would be consideration of the exposure conditions to the patient. We immediately find complex, indeed almost insuperable, problems in defining exposure conditions. Diagnostic ultrasound imaging systems transmit their energy in very brief pulses of mechanical vibration. The frequency, intensity, duration and repetition rate of these pulses varies enormously from one machine to another and the way in which the pulses are scanned through the tissue is also highly variable. Even worse, it is impossible to either predict or measure the dose of ultrasound absorbed at a particular target site. Some attempts at standardization of measurements have been suggested and techniques have been developed for measuring the power output of ultrasound scanners in open water baths. In an attempt to permit comparison between different types of apparatus it has been suggested that the peak powers should be measured at the focal point of the transducer and averaged either over a time encompassing several individual pulses or over the duration of a single pulse. Limited information is now available from a range of different brands of ultrasound equipment and is quoted by Wells (1987). It is staggering to discover that the range of spatial peak temporal average powers has a ratio of 5285 to 1 in a sample of 12 instruments and the same machines show a ratio of 3055 to 1 between the highest and lowest pulse average powers. It is inconceivable that such a huge range of output powers is either necessary or acceptable. If the machines with the lowest powers have been shown to be diagnostically adequate how can one possibly justify exposing the patient to a dose 5000 times greater, even if at this level no definite adverse effects have yet been shown to occur? There is no evidence that the machines with greatest power output produce better quality images, indeed they probably require higher powers in order to compensate for poor system sensitivity. There are as yet no nationally or internationally agreed standards for the output characteristics of diagnostic ultrasound equipment, though the American Institute of Ultrasound in Medicine advises against time averaged powers of greater than 100 mW cm^{-2} (Wells 1987, page 25). There would certainly seem to be room for government guidelines on the output of ultrasound equipment and for legislation making it mandatory for equipment manufacturers to state the output characteristics of their equipment in some standard form.

Whilst considering the potential hazards of ultrasound it is perhaps germane also to consider the evidence concerning its clinical efficacy, especially in obstetrics where it is now so widely applied.

Because the technique has revolutionized our ability to study the entire conceptus there was an early acceptance of the hypothesis that the additional information obtained from an ultrasound investigation must necessarily be of benefit to the patient. Few investigators have actually attempted to confirm this hypothesis and indeed the quantity and quality of information obtained from a diagnostic ultrasound examination has increased and improved markedly over the past few years. Whilst I must agree that it seems reasonable to expect that the information obtained will help in the management of at least some patients, is it not reasonable to expect some sort of proof that the wholesale exposure of populations to often quite significant doses of ultrasound energy is actually of some direct benefit to them? Regrettably the question will probably now not be answered since a properly controlled scientific study can no longer be undertaken as few, if any, obstetricians would agree to forego the early routine ultrasound examination of their obstetric patients.

Whilst considering the clinical efficacy of an ultrasound examination it is pertinent also to consider the arrangements for training and certification of operators. At the present time there is no recognized structured training or certification for the medical users of ultrasound apparatus in the UK and, although some exposure to the technique is now expected as part of the MRCOG and FRCR courses, no attempt is made to examine candidates in their ability to perform and interpret an examination.

The casual observer might be forgiven for wondering why the medical profession is now involved in the wholesale examination of pregnant patients with machines emanating vastly different powers of an energy which is not proven to be harmless to obtain information which is not proven to be of any clinical value by operators who are not certified as competent to perform the examinations.

Having been involved in the performance of obstetric ultrasound examinations myself for almost two decades, I too am convinced that the technique is useful and I am sure it is probably harmless, but I have no scientific evidence to confirm my suspicions.

It is, of course, impossible to prove with absolute certainty that ultrasound is harmless, though the evidence gathered to date is generally reassuring.

Wells (1987) concludes that present research into the possible bio-effects of ultrasound is mostly poorly planned, often poorly controlled and frequently inadequately reported. Surely there is room here for some firm guidance from national or supra-national bodies such as the MRC to ensure that efforts are co-ordinated and planned to approach the whole complex subject systematically?

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British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1123–1135

Incidence and aetiology of hydatidiform mole: an epidemiological review

MICHAEL B. BRACKEN

Summary. Epidemiological investigation of the incidence and aetiology of hydatidiform mole (HM) is receiving increasing attention. Recent, population-based studies suggest that earlier reports of a very high incidence of HM in Asia, Africa and South-Central America may have been exaggerated, due primarily to selection bias in patients studied at university hospitals. Japanese population studies indicate a two-fold higher rate of HM compared with Caucasian rates but Chinese rates appear to be similar. Population studies presently available suggest a worldwide range of HM somewhere between 0·5 and 2·5/1000 pregnancies. When deliveries form the rate denominator the rates are somewhat higher, depending primarily on the national rate of induced abortions. The independent effects on incidence of geographic locale, ethnicity and socio-cultural factors have not been adequately disentangled although the genetic studies suggest ethnicity might be the predominant variable. Maternal age is the most consistently demonstrated risk factor; teenagers and, especially, women over age 35 being at increased risk. The independent effects of paternal age and pregnancy history are not established. Women with a history of one HM seem to have a ten-fold risk of repeat HM compared with women who have no history of HM. Aetiological studies have not revealed any environmental risk factor for which there is unequivocal agreement about its influence on HM. New case-control studies of HM aetiology must classify HM according to genetic aetiology. Cohort studies are required to explore more fully the relation of HM to malignant sequelae.

Epidemiologists have only recently turned their attention to the study of hydatidiform mole (HM). Prompted by dramatic developments in our understanding of the genetic aetiology of this condition, and the hope that study of HM will lead to insights into other reproductive processes, new studies are being conducted at an increasing rate. This review builds upon an earlier one (Bracken *et al.* 1984) which may be consulted by the interested reader. Not all earlier studies are reconsidered. Here the attempt is to integrate the findings of more recent studies. Some of the newer studies are of much more sophisticated design than many earlier ones (although this is by no means always true) and merit considerably more weight.

In addition, the newer studies consider a number of risk factors for the first time. These too are reviewed. However, other aspects have

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not benefited from additional studies; these include seasonal and temporal distributions, socio-economic status, possible parasitic and infectious causes, consanguinity and missed abortion. These topics have been discussed in a previous review by Bracken *et al.* (1984).

Finally, new knowledge concerning the genetic relation of HM to choriocarcinoma has been obtained and the implication of this for future epidemiological studies is considered.

Incidence

Geographic variability

It has been recognized for a long time that the incidence of HM varies in different parts of the world, ranging from 11·5/1000 deliveries in Indonesia to less than 1/1000 deliveries in the United States (Table 1). Asian countries show the highest rates, followed by Africa and Latin America whereas Europe, Australia and the United States generally report the lowest rates. Several methodological issues may account for a proportion of geographic variability in incidence; these are discussed later.

Asian countries appear to report the greatest variability in incidence. The highest rates are reported from Indonesia, the Philippines, and Taiwan although these are usually older hospital-based studies. More recent and better controlled studies from different Japanese prefectures report incidence rates averaging approximately 2·5/1000 pregnancies (Nakano *et al.* 1980; Kawashima *et al.* 1979; Shiina & Ichinoe 1979; Honda *et al.* 1982) (Table 1). In China, a nationwide study found an incidence rate of 0·78/1000 pregnancies (National Co-ordination Research Group of Chorioma (NCRGC) 1980), a rate within the range of those for Caucasians. Among the 23 regions studied in China the incidence ranged from 0·29 (Shanxi) to 1·39 (Zhenjiang) per 1000 pregnancies (NCRGC 1980).

In China high rates have been reported in southern and coastal regions (NCRGC 1980). Urban–rural differences were not found in Guangxi Province (Song *et al.* 1981). Unusually high rates have been reported in selected areas of China, 2·07/1000 pregnancies in Fuski and 3·16 in Tiandeng counties in Nanning, and a rate of 8·83 in Saulian Commune in Jinyuan County, Lishui Region, Zhejiang Province (NCRGC 1980).

African rates have ranged from 1·03/1000 deliveries in Uganda (Leighton 1973) to 4·88/1000 deliveries in Nigeria (Ogunbode 1978). These figures are also based on older hospital-based studies and studies within the same country show highly variable rates, e.g. rates of 1·67 (Ayangade 1979), 2·64 (Agboola 1979), and 4·88 (Ogunbode 1978) per 1000 deliveries in Nigeria.

Latin American studies also range considerably, from 0·23/1000 pregnancies in Paraguay (Rolon & de Lopez 1977) to 4·62/1000 pregnancies in Mexico (Marquez-Monter *et al.* 1968), although another Mexican study (MacGregor *et al.* 1969) reported a much lower rate of 1·63/1000 pregnancies.

Studies from the United States have reported more consistent and generally lower incidence rates, ranging from 0·50 (Douglas 1957) to 1·08 (Hayashi *et al.* 1982) per 1000 pregnancies. Australian studies estimate only slightly higher rates and a recent study from England and Wales an increased rate of 1·54/1000 live births in 1983 (Bagshawe *et al.* 1986) (Table 1).

Within the United States, Hayashi *et al.* (1982) reported differences in the rate of HM per 1000 pregnancies ranging from a low of 0·70 in New England to a high of 1·89 in the Rocky Mountain Census Region. Both China and the United States are large countries with many climatic, geographic and cultural zones. Thus, one might expect more real variability in these countries than in smaller ones. Comparative, population-based data from other large countries, e.g. the Soviet Union and India, are not available.

Racial variability

Racial and geographic variability in incidence are inextricably linked and few studies have adequately disentangled their separate effects. An early study (McCorriston 1968) from Hawaii, a polyracial community, reported that the Japanese accounted for 54% of all trophoblastic disease compared with 14% for Caucasians, although their population sizes were almost equal; however, incidence rates adjusting for pregnancy were not calculated. Another report from Singapore, also a polyracial area, showed little difference in incidence among Malaysians, Chinese, and Indians; however, all rates were much higher than those found in whites (Teoh *et al.* 1971).

In China itself the major ethnic group, the

Table 1. Incidence of hydatidiform mole reported by previous authors

Region	Author(s) and year of publication	Incidence	
		Per 1000 deliveries	Per 1000 pregnancies
North America			
Boston	Hertig & Edmonds (1940)	0·48	
Jersey City	Chelsey *et al.* (1946)	0·76	
New York	Mueller & Lapp (1949)		0·74
Philadelphia	Stroup (1956)	0·67	
New York	Douglas (1957)		0·50
New Orleans	Reiner & Dougherty (1960)	0·45	
Hawaii	McCorriston (1968)		0·75
Rhode Island	Yen & MacMahon (1968)		0·63
Los Angeles	Westerhout *et al.* (1969)	0·90	
New York	Slocumb & Lund (1969)		0·58
Alaska (natives only)	Martin (1978)	3·87	
British Columbia	Yuen & Cannon (1981)		0·83
United States	Hayashi *et al.* (1982)		1·08
United States (Hawaiian white)	Matsuura *et al* (1984)		0·80
Latin America			
Mexico	Marquez-Monter *et al.* (1968)		4·62
Mexico	MacGregor *et al* (1969)	1·97	1·63
Venezuela	Aguero *et al* (1973)		0·92
Paraguay	Rolon & de Lopez (1977)		0·23
Africa			
Uganda	Leighton (1973)	1·03	
Nigeria	Ogunbode (1978)	4·88	
Nigeria (Ogbomoso)	Ayangade (1979)	1·67	
Nigeria (Lagos)	Agboola (1979)	2·64	
Nigeria (Ibadan)	Junaid (1984)	3·04	
Europe			
Norway	Kolstad & Hognestad (1965)	0·77	
Sweden	Ringertz (1970)	0·71	0·64
England (Nottingham)	Elston (1979)	0·65	
Spain	Gomez *et al* (1980)		0·82
Denmark	Vejerslev *et al.* (1984)		0·76
Holland	Franke *et al* (1983)	0·68	0·48
England and Wales	Bagshawe *et al.* (1986)	1·54	
Greenland	Nielsen & Hansen (1979)	1·18	
Australia			
Sydney	Copplestone (1958)		1·20
Sydney	Steigrad (1969)	1·04	0·91
Melbourne	Beischer *et al.* (1970)	1·77	1·41
Asia			
Philippines	Acosta-Sison (1959)	5·00	
Philippines (Manila)	Pelayo & Lopez (1984)	6·80	
Philippines (Quezon)	Baja-Panlilio *et al* (1984)		2·93
Japan	Hasegawa *et al.* (1960)	4·40	
Japan (Wakayama)	Nakano *et al* (1980)	2·55	1·92
Japan (Aichi)	Kawashima *et al* (1979)	2·87	1·92
Japan (Sapporo)	Shiina & Ichinoe (1979)		2·07
Japan (Hokkaido)	Ichinoe *et al.* (1979)		2·79
Japan (Fukushima)	Honda *et al.* (1982)		2·00

Table 1 (*continued*). Incidence of hydatidiform mole reported by previous authors

Region	Author(s) and year of publication	Incidence Per 1000 deliveries	Incidence Per 1000 pregnancies
Asia (*continued*)			
Japan (14 prefectures)	Takeuchi (1984)	3·02	1·96
China	NCRG (1980)		0·78
China	Song *et al.* (1981)		6·67
China (Guangxi)	Shang *et al.* (1982)		0·86
Taiwan	Wei & Ouyang (1963)	8·30	
Hong Kong	Chun *et al.* (1964)	4·10	
Indonesia (Surabaya)	Poen & Djojopranoto (1965)	11·51	9·93
India (Guntur)	Reddy & Rao (1969)		2·17
Malaysia (Kuala Lumpur)	Llewellyn-Jones (1965)		1·31
Malaysia	Ong *et al.* (1978)	1·50	
Singapore	Teoh *et al.* (1971)		1·22
Singapore	Tan *et al.* (1982)	1·15	
Vietnam (North)	Can *et al.* (1983)	0·64	
Israel	Matalon & Modan (1972)	0·75	
Iran	Javey & Sajadi (1978)		3·18
Iraq (Baghdad)	Ghali (1969)	3·62	

Han, have lower incidence rates than the Zhuang within the Guangxi region (0·7 and 1·1/1000 pregnancies, respectively). Inner Mongolian women also have higher rates than the Han (Song *et al.* 1981).

In the United States, blacks have been reported to have a higher incidence than whites in one study (Yen & MacMahon 1968), but a lower rate in two other studies (Westerhout *et al.* 1969; Hayashi *et al.* 1982). Alaskan natives have rates three to four times greater than Caucasian Americans (Martin 1978). Rates for other American Indians are unknown. It may be coincidental that the states with the highest incidence in the United States, the Rocky Mountain states (Hayashi *et al.* 1982), also have the largest population of Indians. Berkowitz *et al.* (1985) have recently reported that Massachusetts residents born outside the United States had a 90% increased risk of HM (RR, 1·9; 95% CI, 1·0–3·6). In Holland, women of Asian origin have also been reported to have greater risk for HM (Kenemans *et al.* 1984).

The incidence of complete moles in Hawaii (Matsuura *et al.* 1984) was greatest in Filipino women (1·75/1000 naturally terminated pregnancies) and Japanese women (1·65) and lowest in Caucasians (0·80) and Hawaiian natives (0·77). The high Filipino and Japanese rates occurred whether they were native or Hawaiian born. The race of the male partner was not a factor when maternal race was taken into account.

Methodological problems in estimating incidence

It is almost certain that some of the observed geographic and ethnic difference in the incidence of HM is due to biased referral of HM patients to major hospitals. In countries where the majority of births occur at home, in nursing homes, or community hospitals, studies based at larger university teaching hospitals will always inflate the incidence estimate because the denominator data (deliveries and, especially, pregnancies) are under-reported. For example, the incidence of HM among deliveries at Surabaya General Hospital in Indonesia, which served poor patients, was 13·9/1000 deliveries (Poen & Djojopranoto 1965). In the Catholic hospital serving private patients in the same city the incidence was 3·03. Since poor people were much more likely to have home births unless a pregnancy developed problems causing it to be referred, this almost certainly accounts for the different hospital-based rates. Recent, similarly high, estimates of HM from the University Hospital in Jakarta, Indonesia (13·0/1000 pregnancies) (Aziz *et al.* 1984) are almost certainly artificially raised for this reason. All of the African studies, for example those from the University Hospitals of Ibadan (Junaid 1984) and Lagos (Agboola & Abudu 1984), suffer from referral bias. In the same way the Philippine data from the University Hospitals of St Tomas in Manila (6·8/1000 live births (Pelayo & Lopez 1984)) and East Ramon in Quezon City (2·93/1000 pregnancies (Bajo-Panlilio *et al.* 1984)) are difficult to assess because of uncertainty about the population base for both the hydatidiform mole cases and pregnancies.

The most reliable incidence estimates derive from the population-based surveys in China (NCRGC 1980), Japan (Takeuchi 1984) and the United States (Yen & MacMahon 1968; Hayashi *et al.* 1982) although local studies which correctly estimate pregnancy rates can be very useful. Pregnancies are used as the denominator in some studies, and deliveries in others. Since all gestations can develop into HM it is preferable to include miscarriages and induced abortions. In many countries this continues to be difficult because of the illegality or inadequate registration of induced abortions. Additionally, spontaneous abortions are under-reported and many occur before pregnancy is recognized. In one survey of cytogenetically verified triploidies, 86% were partial HM (Szulman *et al.* 1981). Since miscarriages are not routinely reported, the incidence of HM will be under-reported to an unknown degree. The incidence of HM in 4829 women seeking induced abortion in the United States was unusually high (1·66/1000) in one study reported by Cohen *et al.* (1979) and low in another (0·75/1000 (Atrash *et al.* 1986)). Possibly women with some pregnancy conditions, e.g. vaginal bleeding and pre-eclampsia, may have sought termination of their pregnancies. Failure to include these patients would also *under*-estimate the incidence of HM. If the rate of HM does not differ in abortions and deliveries then exclusion of abortions will *over*estimate HM incidence, since HM patients are more likely to be referred to hospitals and counted whereas the normal abortions may be excluded from the study denominator.

The clinical classification of HM may vary between studies, some studies are only of benign mole whereas others include invasive mole and even choriocarcinoma. Many studies do not define the criteria used. Differences in histological diagnosis did not explain the high Asian rates of HM compared with the United States (Joint Project for Study of Choriocarcinoma and Hydatidiform Mole in Asia (JPSCHMA) 1959); however, this study did not account for selection bias due to most Asian deliveries occurring at home.

Although it is widely believed that Asians have higher HM rates than Caucasians, only the Japanese rates are satisfactorily investigated and they are about double those from the United States and Europe. The Chinese rates appear to be the same as the Caucasian rates. The extraordinarily high rates reported from the Philippines, Indonesia and parts of Latin America are almost certainly exaggerated for reasons stated above and more precise population-based estimates have not been reported. Similarly, there are no reliable data from Africa or any countries of the Third World, and there are unlikely to be reliable data until census-based comprehensive pregnancy reporting systems are established in these countries. Some racial variability in the incidence of HM is highly likely, especially in light of the genetic aetiology of HM described below. Unfortunately, the true variability can at present only be glimpsed through the methodological biases of much of the extant literature. The following sections review some other variables used to characterize the incidence of HM.

Incidence by maternal age

The risk factor most consistently associated with HM in all ethnic groups and geographic regions is maternal age. Studies in Italy (Villani *et al.* 1981; La Vecchia *et al.* 1984), Greenland (Nielsen & Hansen 1979), China (Song *et al.* 1981), Japan (Nakano *et al.* 1980; Kawashima *et al.* 1979; Shiina & Ichinoe 1979; Honda *et al.* 1982), Britain (Stone & Bagshawe 1979), and the United States (Hayashi *et al.* 1982) all suggest an increased risk in women over the age of 35 with a further five-fold (Matsuura *et al.* 1984; La Vecchia *et al.* 1984) or ten-fold (Yen & MacMahon 1968; Matalon & Modan 1972; Bagshawe *et al.* 1986) increase beyond the age of 40.

Teenagers have recently been shown to have moderately elevated rates of HM in the United States (Hayashi *et al.* 1982), Britain (Bagshawe *et al.* 1986; Stone & Bagshawe 1979), Greenland (Nielsen & Hansen 1979) and Italy (La Vecchia *et al.* 1984).

Incidence by paternal age

The age of the father has been much less studied. It was unrelated to incidence in three United States studies (Yen & MacMahon 1968; Matsuura *et al.* 1984; Messerli *et al.* 1985). A recent Italian study (La Vecchia *et al.* 1984) reported an increased risk to fathers over age 45 (RR, 3·6; 95% CI, 1·1–12·2) after adjustment for maternal age. When smoking was also controlled the risk was further increased to 5·7 (95% CI, 1·9–16·8). Thus, this study found independent age effects for both mothers and fathers, but a stronger effect for the latter. Unfortunately, the Italian study suffers from the inclusion of some patients with choriocarcinoma among the HM series. The *difference* between maternal and paternal ages was not a risk factor in a Japanese study (Sasaki *et al.* 1979).

Incidence by menarcheal age

A good deal of recent interest has been shown in the association of menarcheal age with subsequent reproductive outcomes, especially risk of miscarriage (Bracken *et al.* 1985). In Massachusetts (Berkowitz *et al.* 1985) and Baltimore (Messerli *et al.* 1985) menarcheal age was found to be unassociated with HM. In the Baltimore study there was also no relation between length of menstrual cycle or duration of menses before pregnancy (Messerli *et al* 1985).

Incidence by pregnancy history

Data on this risk factor are inconclusive. Much of the literature confuses the two variables gravidity (total previous pregnancies) and parity (deliveries) Very few studies have accounted for any of the correlated variables of maternal age, age at first pregnancy, previous induced abortions or miscarriage, interpregnancy spacing and history of infertility. No studies have examined all of them. In Rhode Island (Yen & MacMahon 1968) and Italy (La Vecchia *et al.* 1985) parity was not associated with HM after adjustment for maternal age. Age at first pregnancy was unrelated to HM in Baltimore but a history of miscarriage was (Messerli *et al.* 1985). However, in other studies a history of miscarriage (Berkowitz *et al.* 1985; La Vecchia *et al.* 1985) and repeated miscarriages (La Vecchia *et al.* 1985) have been reported to be unrelated to HM. However, another analysis of the Italian data (Parazzini *et al.* 1985) found an elevated risk of HM in nulliparous women with a history of miscarriage. In the Italian study (La Vecchia *et al.* 1985), difficulties in conception were significantly more common preceding the HM (RR, 3·7; 95% CI, 1·9–7·5) but a history of infertility and menstrual problems was unrelated in Baltimore (Messerli *et al.* 1985). A recent report from Australia (Olesnicky & Quinn 1984) indicated an increased rate of HM after artificial insemination by donor (AID) compared with normally conceived pregnancies (2·70/1000 conceptions and 0·83/1000 live births respectively, $P = 0{\cdot}025$). If early pregnancy loss after AID is adjusted, then the difference in their risk is even further increased. It will be of great interest to see if other series of AID pregnancies report similarly elevated rates.

Repeat hydatidiform mole

Sand *et al.* (1984) have detailed the rate of repeat HM in a large series of patients in Chicago. They calculate a 1·3% repeat rate of second HM (over 10 times the expected rate of first HM). The authors also calculated a 1·3% repeat rate from 17 previous studies (45 repeat HM among 3354 first cases). Overall 14% needed chemotherapy for the initial mole and 32% for the second event leading them to conclude that 'an increasing degree of invasiveness' occurred 'with subsequent gestational trophoblastic disease episodes'. Specifically, 19 first benign moles were followed by another benign mole in 12 patients, by an invasive mole in three, and by choriocarcinoma in four. Two first invasive moles and one choriocarcinoma were each followed by a benign mole. La Vecchia (1985) also found that 5 of 100 women with trophoblastic disease had a history of trophoblastic disease compared with only 1 of 200 age-matched women having a normal pregnancy. The five previous episodes included one partial HM, three complete HM, and one choriocarcinoma. In Holland 3 of 283 patients (1·1%) had a history of HM (Franke *et al.* 1983), over 18 times the rate in the normal population. In the Chicago study (Sand *et al.* 1984) the risk for a third trophoblastic event rose to 28%. In England and Wales a 1·3% repeat rate per pregnancy of risk has recently been reported for second HM and 15·4% for a third HM (Bagshawe *et al.* 1986).

Aetiological hypotheses

Nutritional factors

Several early studies considered nutrition, although the results have been equivocal (see Bracken *et al.* 1984 for review), and are inextricably linked with socio-economic status. Most recently Berkowitz *et al.* (1985) reported that dietary carotene above the median level of consumption in the control group appeared to reduce the risk of HM (RR, 0·6; $P = 0{\cdot}02$). A significant trend for decreasing risk with increasing consumption of carotene and animal fat was also noted. Protein intake was not associated with HM. Other recent studies have found no association of diet or nutritional status (measured in very general terms) with HM (MacGregor *et al.* 1969; Shang *et al.* 1982; Llewellyn-Jones 1965) although carotene was not studied.

Environmental agents

Increasing attention has focused for the first time on several environmental agents as risk factors for HM. Surprisingly, cigarette smoking has been examined in only two very recent studies. La Vecchia (1985) found that duration of smoking was positively associated with increased risk. Compared with women who never smoked the increased risk of HM was 1·3 for women smoking <5 years, 2·3 for 5–9 years, and 4·2 for ≥10 years. Berkowitz *et al.* (1985) found no increased risk for smoking before or during the pregnancy. However, duration of smoking was not examined.

Recently, use (ever, duration or recency) of oral contraception has been found to be unrelated to risk of HM (Berkowitz *et al.* 1985; Messerli *et al.* 1985; La Vecchia *et al.* 1985). There is one case report of a woman experiencing two molar pregnancies following bromocriptine therapy (Ogborn 1977). Whether this is due to the therapy, or associated with the underlying difficulty in conceiving—as found by La Vecchia (1985), or is just a chance association, is unclear.

Previous use of an intrauterine contraceptive device (IUCD) was significantly associated with HM in the Italian study (La Vecchia *et al.* 1985) (RR, 3·7; 95% CI, 1·1–12·0) but less strongly related in that by Berkowitz *et al* (1985) (RR, 1·7; 95% CI, 0·9–3·1) and unrelated in Baltimore (Messerli *et al.* 1985). Berkowitz *et al.* (1985) also found contraceptive failure of spermicides and other methods did not increase risk of HM although the numbers of exposed subjects are very small.

Two of 129 daughters of mothers who used diethylstilbestrol in pregnancy developed HM (Schmidt *et al.* 1980). The incidence (15·5/1000 pregnancies) is very high but is based on two exposed cases and merits further study. Another study found no relation to DES exposure (Messerli *et al.* 1985).

Constable & Hatch (1985) have recently reviewed several studies from South East Asia which address the question of whether exposure to herbicides (primarily Agent-Orange) are associated with an increased risk of HM. Two studies from South Vietnam consider maternal exposure. L. D. Huong and N. T. N. Phuong (unpublished observations) provide rates of HM (and choriocarcinoma) seen in patients at the Gyneco-Obstetrical Hospital of Ho Chi Minh City (formerly Tu Du Hospital in Saigon). Figure 1 shows the incidence of HM and choriocarcinoma from 1952 to 1981. Data are taken from a variety of sources including doctoral theses and administrative data. The rate of HM and choriocarcinoma changed from 8·6/1000 pregnancies in 1952 (all the data have been recalculated from the original Vietnamese paper which contained computational errors) to 8·7 in 1971 after which it rose to 45·4 in 1979, declining only slightly in the following 2 years. The early Vietnamese rates, therefore, are higher than reported from anywhere except Indonesia (Poen & Djojopranoto 1965), the study reviewed

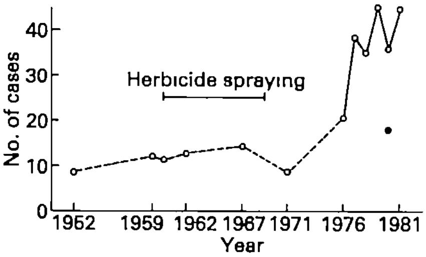

Fig. 1. Cases of hydatidiform mole and choriocarcinoma per 1000 pregnancies reported in two Vietnamese studies. Data from (Tu Du) Gynaeco-Obstetrical Hospital, Ho Chi Minh City (Saigon) (L D Huong & N. T. N. Phuong, unpublished observations) (○) and Tay Ninh Polyclinic Hospital (●)

above. The rates after 1971 are the highest reported anywhere in the world.

L. D. Phuong and N. T. N. Huong (unpublished manuscript cited in Constable & Hatch 1985) reported a case-control study of 100 HM cases and 284 age and parity matched controls. Past herbicide exposure was ascertained at interview and reported by 56·5 and 9·8% of cases and controls respectively ($P<0·001$). HM patients were also likely to report having a 'good' living standard (86% *v.* 45%) having husbands who smoked (84% *v.* 70%) and who drank alcohol (90% *v.* 35%). No details are provided on how these measures were quantified or assessed.

Since most deliveries in Vietnam are in district dispensaries the Vietnamese data almost certainly suffer from selection bias. It is uncertain what accounts for the reported epidemic of HM occurring after 1971. The period of herbicide spraying is depicted in Figure 1. If herbicides were to influence directly the development of HM one would expect the epidemic and spraying to be more closely linked in time. It is possible that war-time conditions prevented complete reporting of HM or disrupted normal referral patterns of complicated pregnancies to Saigon. Another hypothesis is that herbicides enter the food chain and take several years to affect reproductive processes. Yet another possibility must be that consideration of reproductive problems being due to herbicides only reached public attention in Vietnam in the mid 1970s and this publicity further enhanced referral of molar pregnancies to the Gyneco-Obstetrical Hospital. Interestingly, the rate of HM at Tay Ninh City Polyclinic, another referral hospital, in the early 1980s was 18/1000 deliveries (reported by Constable & Hatch 1985). Other data from South Vietnam support the maternal herbicide exposure hypothesis. L. D. Phuong and N. T. N. Huong (unpublished manuscript cited in Constable & Hatch 1985) compared the effects of herbicides on the rate of molar pregnancy in a sprayed village with that in the 10th district of Ho Chi Minh City where 92% of women were considered unexposed. The time period covered is unknown, but the HM rates (18·2 and 3·9 per 1000 pregnancies (recalculated from Constable & Hatch 1985)) are significantly different (RR, 4·67; 95% CI, 3·20–6·82). It is unlikely that the conflicting explanations will ever be satisfactorily resolved in retrospect. However, prospective monitoring of the incidence of HM with proper control groups and accurate denominator data would be useful.

The effect of herbicide exposure on the father has been assessed in North Vietnam (Can *et al.* 1983 cited by Constable & Hatch 1985). Three unsprayed areas (one in the mountains, one lowland, and one coastal) were studied. Exposure to herbicide in husbands occurred during their war service in the southern (sprayed) areas of Vietnam. The rate of HM per 1000 pregnancies was 0·87 (28 of 32 069) in the exposed couples and 0·58 (70 of 121 993) in the unexposed (RR, 1·52; 95% CI, 0·99–2·35). As far as we can tell from the available sources this was a relatively well-conducted survey using trained interviewers. However, maternal age, parity and other important variables were not controlled. Moreover, Constable & Hatch (1985) pointed out that most conceptions would have occurred more than 80 days after exposure, the period of time that sperm survive What is, perhaps, most interesting about this population-based study is the overall rate of HM observed in the study areas (0·64/1000 pregnancies) which is much lower than the hospital-based rates, thus providing evidence for selection bias in other Vietnamese hospital-based studies.

None of the studies conducted in the United States or Australia on the veterans' exposure to herbicides has considered HM as a reproductive outcome of interest (Pearn 1983; Erickson *et al.* 1984; Friedman 1984).

Familial occurrence

One study reported three families in India each having two or more sisters with HM in one or more pregnancies (Ambani *et al.* 1980). La Vecchia *et al.* (1985) reported one molar pregnancy in Italy with a history of HM in 4 of 100 relatives of the woman (3 complete HM, 1 choriocarcinoma) and in 1 of 100 relatives of the father (complete HM) compared with no family history among 200 age-matched controls.

Genetic aetiology

Vassilakos *et al.* (1977) proposed that HM consisted of entities distinguishable on morphological and cytogenetic criteria. *Complète HM* never contains an embryo, umbilical cord, or amniotic membranes, and all the chorionic villi are abnormal, and it is usually sex chromatin-positive with a 46XX chromosome constitution. *Partial HM* contains an embryo, umbilical cord, and amniotic membranes, and has some chorionic villi containing fetal vessels. Its chromosomes are almost always triploid although rarely other chromosome abnormalities have been found.

The inheritance of molar chromosomes was studied by Kajii & Ohama (1977). Complete moles are androgenetic in origin, receiving all chromosomes (including both X chromosomes) from the father. These studies have been confirmed in Hawaii (Jacobs *et al.* 1978), Japan (Wake *et al.* 1978), and England (Lawler *et al.* 1979). Partial moles, on the other hand, contain a maternal contribution to the karyotype. Most, if not all, partial moles are triploid and of dispermic origin (Vassilakos *et al.* 1977). Diandry (an extra paternal set of chromosomes) rather than digyny (an extra maternal set} is found in most partial moles (Szulman *et al.* 1981; Lawler *et al.* 1982*a*; Jacobs *et al.* 1982).

Origin of complete moles

Three methods of fertilization are possible for the complete mole.

First, fertilization may be by dispermy. This would produce an androgenetic conceptus which is heterozygous for many loci which are also heterozygous in the father. Biochemical and cytogenetic evidence indicates that heterozygous (dispermic) moles account for 5–10% of complete molar pregnancies (Ohama *et al.* 1981; Yamashita *et al.* 1981; Fisher & Lawler 1984).

Second, fertilization may be by a diploid sperm. However, this has never been demonstrated and this method of origin appears extremely unlikely (Lawler *et al.* 1979, 1982*b*).

Third, the most likely method of fertilization of complete HM is by a normal haploid spermatozoan whose nuclear material replicates in the ovum without subsequent cell division, thus restoring the diploid number of 46. YY zygotes are lost, presumably during early cleavage. That the majority of complete moles are monospermic has been shown by study of biochemical polymorphisms (Kajii & Ohama 1977; Jacobs *et al.* 1978; Wake *et al.* 1978) and by observations that human leucocyte antigen specificity is homozygous in complete HM (Yamashita *et al.* 1981; Ichinoe *et al.* 1981; Jacobs *et al.* 1980).

Malignant potential of hydatidiform moles

Recent studies have suggested that complete, but not partial, HM is associated with the well-known increased risk of choriocarcinoma (Bagshawe *et al.* 1986; Stone & Bagshawe 1979; Vassilakos *et al.* 1977; Berkowitz *et al.* 1979; Lee *et al.* 1981; Insler *et al.* 1981). Kajii (1980) first suggested that the rarer heterozygous moles were more likely to require chemotherapy. Subsequent studies support this view (Fisher & Lawler 1984; Davis *et al.* 1984; Wake *et al.* 1984). Recently, Bagshawe *et al.* (1986) have discussed the clinical management of sequelae to HM.

Future studies

Advances in our understanding of the genetic aetiology of HM have created an opportunity for new epidemiological studies. HM must be classified in future epidemiological studies as being partial or complete, either by detailed genetic analyses of the mole and both parents or, less expensively, by clinicopathological analysis that has been validated by cytogenetics. Additionally, complete moles should be classified as to their hetero- or homozygous origin if epidemiological studies are to be done of the risk factors for future malignancy.

Racial difference in incidence may reflect inherited variability in susceptibility to conception errors, specifically to loss of DNA in the ova. The strong maternal age effects suggest a systematic increase in the probability of error in both immature and postmature ovaries, such as occurs with Trisomy 21 (Janerich & Bracken 1986). Thus, a maternal age effect for complete HM would be expected but not for partial moles due to dispermy, since risk of triploidy appears to be unrelated to maternal age (Hook 1984) A recent analysis of Italian data supports this hypothesis (Parazzini *et al.* 1986).

Other possible risk factors for errors in conception need to be examined, especially environmental exposures, including those related to the occupations of both parents. Smoking, alcohol and caffeine are known in-vitro mutagens and their maternal use is worth further investigation. Delayed ovulation or fertilization may both lead to 'over ripe' ova which may be more susceptible to dispermic fertilization, and some contraceptive practices may increase the risk for delayed ovulation (oral contraceptives) or delayed fertilization (rhythm method) (Bracken & Vita 1983). Thus, detailed examination of contraceptive histories is appropriate. Reproductive monitoring of toxic waste sites and other environmentally hazardous locations should include HM as an outcome variable.

Because HM is relatively rare, the case-control design will be the method of choice for aetiological studies (Bracken 1984). Since maternal age and race are reasonably well established risk factors, investigators may prefer to match on them in order to increase their chance of finding other important risks Case ascertainment should be prospective, both to permit genetic classification and to avoid under ascertainment. Retrospective data collection, even when done very thoroughly, has been shown to miss up to 75% of all partial moles (Bracken *et al.* 1984). Studies of HM as a risk factor for choriocarcinoma, however, should prospectively follow up a cohort of HM patients, since approximately 2–19% of women with HM will experience malignant sequelae (Matalon *et al* 1972) within an average period of about 1 year It is most important to determine what, if any, ethnic and geographic variation exists in the rate of malignant sequelae to HM and what other factors might increase the risk of their development.

Acknowledgments

I am grateful to Professors K. D. Bagshawe and S. D. Lawler for their comments on an earlier draft of this manuscript and to Ann Wetherbee, Mary Tinker and Mary Jo Shepard for their administrative assistance Partial support was provided by the National Institute of Child Health and Human Development Award HD 16282 and the National Perinatal Epidemiology Unit.

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British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1136–1142

Nifedipine as a second line antihypertensive drug in pregnancy

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Summary. Slow-release nifedipine has been used in the treatment of severe hypertension in 23 pregnant women. In 22 this was in combination with other drugs, in 18 including atenolol. Good control of blood pressure was achieved in 20 women. The perinatal mortality of the group was 130/1000, with a high caesarean section rate (71% of livebirths), a high rate of abnormal CTGs, a high rate of premature delivery, and a high rate of infants who were small-for-dates. Whether this is due to the disease process or the medication is uncertain. For the present time these combinations should only be used in severe hypertensives or in the context of a controlled trial.

Nifedipine is a calcium channel blocking drug, widely used in non-pregnant patients in the treatment of angina and the acute and chronic treatment of hypertension. In the latter roles it has proved very effective (Bertel *et al.* 1983; Murphy *et al.* 1983) but mild side-effects such as headaches, flushing and ankle swelling have become apparent (Gill *et al.* 1986); they are rarely troublesome.

Its use in obstetrics has been limited, and is still to a large extent experimental. It has been used as a tocolytic agent (Ulmsten *et al.* 1980; Read & Wellby 1986), and one trial included patients with hypertension (Ulmsten 1984). In acute hypertensive situations in pregnancy and the puerperium, oral or sub-lingual capsules have been shown to be effective, rapid in onset, and to cause no deterioration in the fetal heart recording (Walters & Redman 1984). It has been used in severe pre-eclampsia, for periods of up to 8 days (Greer *et al.* 1986), as a second line treatment when labetalol alone had failed to control the blood pressure.

The treatment of essential hypertension in pregnancy is controversial, aggressive treatment (Rubin *et al.* 1983) and no treatment at all (Naden & Redman 1985; Mabie *et al.* 1986; Sibai *et al.* 1983) having their advocates. Our policy is to treat all women with essential or non-proteinuric gestational hypertension with atenolol (Rubin *et al.* 1983), unless there are contraindications or delivery is a reasonable alternative. Over the past 3 years, sustained-release nifedipine has been used as a second line drug in the treatment of resistant hypertension in pregnancy, when atenolol alone has failed to reduce the maternal blood pressure to ≤ 140/90 mmHg. This report summarizes our experience with particular regard to treatment efficacy and safety.

Patients and methods

Between 1982 and 1986, 110 pregnant patients with essential or non-proteinuric gestational hypertension were managed jointly in the antenatal clinic by a consultant physician and a consultant obstetrician. We define essential hypertension as a blood pressure of ≥ 140/90 mmHg outside pregnancy or in the first trimester, gestational hypertension as a rise of ≥ 30/15

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mmHg above the levels in early pregnancy, and pre-eclampsia as gestational hypertension with the addition of proteinuria of at least 500 mg/ 24 h.

All women with a blood pressure of ≥ 140/95 mmHg on at least two occasions were treated with atenolol, unless delivery was considered a suitable alternative or atenolol was contraindicated. In those women where β-blockade was contraindicated methyldopa was normally used as first line management. Treatment was commenced with atenolol (50–100 mg rising as needed to 100–200 mg/day) in 75 patients, and with methyldopa (750–2000 mg/day) in 14. One asthmatic patient received slow-release nifedipine (40 mg/day) as initial treatment.

Additional antihypertensive treatment was required in 35 patients, 22 of whom received combinations including slow-release nifedipine (40–120 mg/day). In 11 patients this was in combination with atenolol alone, in 4 with methyldopa alone, and in 7 in combinations including atenolol. A total of 23 women thus received slow-release nifedipine as a hypotensive agent in pregnancy. In no women was nifedipine given in the first trimester.

Clinical profiles are summarized in Table 1. The median age of the 23 patients was 32 years (range 19–39 years); four patients were nulliparous. Six patients were black, 13 Asian and four white. Eleven patients had previous pregnancy losses, three stillbirths and eight abortions. In addition three of the women had had neonatal deaths in previous pregnancies. There were 14 women with essential hypertension, four with gestational hypertension, three with pre-eclampsia superimposed on essential hypertension, one woman with systemic lupus erythematosus (SLE), and one with hypertension associated with presumed chronic pyelonephritis. Of the 19 multiparous patients 17 had at least one previous pregnancy complicated by hypertension (range 1–5).

Table 1. Clinical features of patients

Patient no.	Age (years)	Ethnic origin	Previous pregnancies		Hypertension diagnosis
			Successful	Unsuccessful*	
1	27	Black	1(1)	2 Miscarriages	Essential
2	36	Asian	2	0	Essential
3	27	Black	1(1)	0	Renal†
4	19	White	0	0	Gestational
5	39	Asian	1	1 NND (1)	Essential
6	25	Asian	0	0	Gestational
7	29	Asian	2(1)	0	Essential
8	24	White	0	0	Essential
9	33	Black	3(3)	0	Essential
10	36	White	3	1 NND (1)	Essential
11	27	Asian	2(2)	1 Miscarriage	Gestational
12	34	Asian	0	0	Gestational
13	28	Asian	4(2)	1 SB	Essential
14	22	Asian	3(1)	0	Essential/pre-eclampsia
15	33	Asian	1	2 SB 1 NND (1)	SLE
16	32	Asian	4(2)	2 Miscarriages	Essential/pre-eclampsia
17	37	Black	2(1)	2 Miscarriages	Essential
18	35	White	5(2)	2 Miscarriages	Essential
19	28	Asian	1(1)	0	Essential
20	30	Black	1(1)	0	Essential
21	32	Asian	2(2)	2 Miscarriages	Essential/pre-eclampsia
22	39	Black	5(5)	1 Miscarriage 1 SB	Essential
23	39	Asian	2	8 Miscarriages	Essential

SB, Stillbirth, NND, neonatal death; SLE, systemic lupus erythematosus.

* Miscarriage includes ectopic pregnancies.

Figures in brackets are pregnancies complicated by hypertension

† Thought to have chronic pyelonephritis

Prospective records were kept of the progress of all patients. Blood pressure was measured seated after 2 min rest at each antenatal visit, and if an inpatient at 6-h intervals. In outpatients a Hawksley Random Zero sphygmanometer was used. The diastolic blood pressure was taken at the fourth phase (muffling of sounds). Ultrasound estimation of fetal growth was made at 2-week intervals, and fetal cardiotocographs (CTG) were recorded as indicated. Regular estimations were made of serum urate, and if proteinuria was present on ward testing, this was quantified. Admission and delivery were dictated by the fetal and maternal conditions. All infants were examined in the neonatal period by a paediatrician, with special regard to growth, Dubowitz score and fetal abnormality.

Results

Table 2 gives details of the booking, pre- and post-nifedipine and predelivery blood pressures. The pretreatment blood pressure was taken, as described previously, at the visit at which the decision to commence nifedipine was taken. The post-treatment blood pressure was taken in the same manner 7 days later, and the predelivery blood pressure when the decision to deliver the baby was taken. The dose of nifedipine at delivery, duration of nifedipine treatment and other antihypertensive medication at delivery are also shown. The addition of nifedipine to the antihypertensive regimen was effective in controlling the blood pressure in 20 patients, the mean pre- and post-nifedipine blood pressures being 149/98 mmHg (SD 11/6) and 132/81 mmHg (SD 17·6/14) respectively. Three patients appeared particularly sensitive to the addition of nifedipine (nos 9, 13, 15), with large falls in blood pressure; the drug was stopped in only one patient (no. 9) although it was reintroduced later in pregnancy due to high blood pressure when again hypotension developed on a total daily dose of 80 mg/day. In patient 13 the nifedipine was stopped, and in patient 15 the atenolol was stopped due to fetal bradycardia. In two patients the nifedipine was stopped because of possible

Table 2. Details of treatment

		Blood pressure (mmHg)				Nifedipine	
Patient no.	Other drugs at delivery	Booking	Pre-nifedipine	Post-nifedipine	Delivery	Dose at delivery (mg)	Duration of treatment (weeks)
1	Atenolol	130/80	142/94	130/80	148/98	40	2
2	Atenolol	130/75	152/102	126/82	146/80	40	2
3	Atenolol	140/90	140/90	130/80	138/104	80	24
4	Atenolol	125/70	146/104	132/78	134/84	80	5
5	Atenolol	150/90	162/90	120/80	130/80	80	11
6	Atenolol	120/80	132/96	128/82	146/82	40	19
7	Atenolol	150/90	140/94	136/90	150/95	40	8
8	Atenolol	140/90	162/94	150/96	154/98	80	5
9	Atenolol	150/90	133/94	84/50	84/44	80	4
10	Atenolol	130/90	148/90	138/84	150/85	40	11
11	Atenolol	140/80	160/100	120/80	120/80	40	1
12	Methyldopa	120/70	172/100	160/95	140/90	80	7
13	Methyldopa	147/112	140/107	104/58	134/86	0	6*
14	Methyldopa	110/80	150/110	130/90	140/95	80	14
15	Methyldopa	150/90	146/104	114/50	112/70	80	18
16	Atenolol + methyldopa	120/85	140/100	140/80	170/110	120	2
17	Atenolol + methyldopa	170/110	130/94	140/72	130/85	40	3
18	Atenolol + methyldopa	140/80	156/96	154/96	168/100	0	1*
19	Atenolol + methyldopa	140/90	146/94	164/68	160/100	120	20
20	Atenolol + hydralazine	150/105	144/96	144/102	144/102	40	2
21	Atenolol + hydralazine	140/80	170/110	120/90	130/90	80	5
22	Atenolol + hydralazine	200/120	150/100	130/85	138/80	80	16
23	None	140/90	154/103	132/96	126/86	40	15

* Indicates that treatment stopped because of possible side-effects See text for details.

maternal side-effects: patient 13 was vomiting, and patient 18 had ankle oedema.

Table 3 details the outcome of the pregnancies. The mean gestation at delivery was 35 weeks (range 29–39). Of the 21 live born infants, 15 (71%) were born by caesarean section, six of them because of a poor antenatal cardiotocograph. Antenatally a poor CTG was defined as a trace with a score of ≤ 3 on the system of Pearson & Weaver (1978). During labour or attempted induction, persistent variable or late decelerations were noted in two women leading to delivery by caesarean section. One woman with a poor antenatal CTG had a vaginal delivery.

The relation between birthweight and ethnic origin has been widely commented upon (McFadyen *et al.* 1984; Taha *et al.* 1984; Dawson *et al.* 1982; Barron 1983). When other variables were corrected for, there was no difference between the birthweights of babies of European and Moslem women, although Hindu women had babies approximately 190 g lighter (McFadyen *et al.* 1984). This difference appears to become apparent only after 36 weeks gestation (Dawson *et al.* 1982). Commonly used centile charts were derived from a European population (Gairdner & Pearson 1971). Others give corrections for maternal weight and height (Thomson *et al.* 1968; Altman & Coles 1980), and might be more accurate in a multiracial situation, although they do not apply until 33 weeks gestation. For the purpose of this study, centile values were obtained from the charts published by Gairdner & Pearson (1971) noting the comments made above. Accepting these limitations it can be seen that of the 22 infants with assessable data, 9 (41%) were on or below the 3rd

Table 3. Outcome of pregnancies

Patient no.	Gestation at delivery (weeks)	Mode of delivery	CTG	Estimated blood loss (ml)	Birthweight			Outcome
					g	Centile	Corrected centile	
1	38	Vaginal	N	150	2700	10	<3	A
2	37	Caesarean	PA	300	2310	5	5	A
3	34	Vaginal	N	350	1500	<3	1	A
4	37	Vaginal	PA	250	2460	10	8	A
5	31	Caesarean	PA	400	960	<<3		A
6	34	Caesarean	PA	600	1660	3	<3	A
7	39	Vaginal	N	50*	2790	10	1	A
8	38	Vaginal	N	400	2200	3	2	A
9	33	Caesarean	PA	500	1660	5	1	A
10	39	Caesarean	N	700	2740	10	10	A
11†	31	Vaginal						SB
12	39	Caesarean	N	400	3460	50	75	A
13	33	Caesarean	N	400	1600	<5	5	A
14	33	Caesarean	PL	600	1280	<3	10	A
15	36	Caesarean	PL‡	700	2080	5	1	NND
16	29	Caesarean	N	500	1610	>50		A
17	36	Caesarean	N	500	1920	3	1	A
18	35	Caesarean	PA	500	2030	5	10	A
19	36	Caesarean	PL	300	1820	<3	<3	A
20	38	Caesarean	N	500	2840	10	16	A
21	33	Caesarean	N	300	1000	<<3	2	A
22	30	Vaginal		500	600	<<3		SB
23	39	Vaginal	N	250	2700	10	10	A

Abbreviations used: CTG, cardiotocograph; N, normal CTG; PA, poor antenatal CTG, PL, poor CTG in labour (for definitions see text).

Outcome: A, alive, SB, stillbirth; NND neonatal death

* Patient no 7 had a secondary postpartum haemorrhage due to retained placental fragments.

† Patient no. 11 had a premature stillbirth at home.

‡ Infant no. 15 had congenital heartblock due to maternal SLE

birthweight centile, and only 2 (9%) achieved the 50th centile. For the 19 deliveries which occurred at 33 weeks or later, the centile values were also derived taking into account maternal height and weight (Altman & Coles 1980). Ten (52%) were below the 3rd centile, only one exceeding the 50th.

Fourteen babies (67% of live births) required admission to the special care unit for varying periods of time. One was subsequently transferred elsewhere due to congenital heartblock associated with maternal SLE and died (no. 15). No unexpected problems were encountered in the remainder, with the exception of no. 21. This baby was found to be thrombocytopaenic shortly after birth, and has subsequently developed a left hemiplegia.

Discussion

No data have yet been reported on long-term use of calcium channel blocking agents in human pregnancies. Our data relate to 23 women who received such therapy with slow-release nifedipine for a mean interval of 8·75 weeks (range 1–24). Of the 23 women, 13 (57%) were Asian, 6 (26%) black, and 4 (17%) white. This distribution differs significantly from that of the total antenatal population (45% Asian, 15% black, 40% white).

The addition of nifedipine to the antihypertensive regimen was effective in controlling the blood pressure in 20 patients, the mean pre- and post-nifedipine blood pressures being 149/98 mmHg (SD 11/6) and 132/81 mmHg (SD 17.6/14) respectively. These data suggest the slow-release preparation of nifedipine to be an effective anti-hypertensive agent in pregnancy.

There were three perinatal deaths, a perinatal mortality rate of 130/1000. These include one death secondary to congenital heartblock associated with maternal SLE, one delivery at home where the baby was dead when the ambulance arrived, and one intrauterine death in a woman with a poor obstetric history. Others have reported on the treatment of essential hypertension in pregnancy, and the fetal outcome associated with different therapeutic regimens (Kincaid-Smith *et al.* 1966; Lieberman *et al.* 1978; Eliahou *et al.* 1978; Arias & Zamora 1979; Bott-Kanner *et al.* 1980; Rubin *et al.* 1982; Sibai *et al.* 1983; Mabie *et al.* 1986). Measured in terms of perinatal mortality, and comparing our results with these studies, the combination would appear to be useful.

Nifedipine is known to be a potent uterine relaxant, and might be expected to give rise either to hypotonic uterine action in labour or postpartum haemorrhage. Estimation of blood loss at delivery or caesarean section is notoriously inaccurate, but we noted no excess haemorrhage in our treated patients. In eight patients having vaginal deliveries no instances of hypotonic uterine action were noted.

Differing populations and selection criteria make comparison with other series difficult, but our group of women appears to have had a high caesarean section rate (overall 65%, live births 71%), a high rate of abnormal CTGs, a high rate of preterm delivery, and a high rate of infants who were small-for-dates. There was no definite pattern of growth retardation as analysed by crown–heel length and head circumference measurements. The results are particularly hard to assess as they are derived from a highly selected, high risk, multiracial group of patients whose blood pressure was not controlled by first line therapy. There did not appear to be any difference in fetal characteristics between the groups treated initially with atenolol and methyldopa, although the numbers in the methyldopa group were very small.

Bott-Kanner *et al.* (1980) reviewed their experience of treating resistant essential hypertension in pregnancy with the combination of propranolol and hydralazine. These data show fewer caesarean sections and babies born at a later stage of gestation fewer of whom were small-for-dates. Are the results in our series therefore the result of the disease process or the treatment?

The use of nifedipine as a single agent in pregnancy has been explored in animal studies (Veille *et al.* 1986; Golichowski *et al.* 1985), although they have used far higher doses than are given clinically. In single agent form it appears not to alter uterine blood flow appreciably, and not to cause excessive hypotension. These studies looked at the acute use of the drug, and indeed the studies in man outlined earlier did not explore the chronic use of nifedipine, the average duration of treatment being around 8 days, in combination with methyldopa or labetolol. In addition to the studies referred to previously, nifedipine has been employed in other uncontrolled studies reported recently at the Congress of the International Society for the study of Hypertension in Pregnancy (Dulitzky *et al.* 1986; Martinelli *et al.* 1986). These studies contain a mixture of patients with essential and gestational hypertension, and pre-eclampsia. The consensus of opinion of these groups appears to be that nifedipine used alone is safe and effective in pregnancy.

One unpublished study has looked at the effect of an intravenous infusion of propranolol to a pregnant ewe, whilst the fetal lamb was infused with nifedipine (Naden & Redman 1985). Whilst the doses were above those given in human treatment, the individual drugs given alone appeared to have no detrimental effects. When combined, however, acidosis appeared in the fetal lamb. One preliminary report has appeared concerning the use of the combination of atenolol and nifedipine in the management of severe pre-eclampsia (Rubin *et al.* 1984). The mean duration of treatment with nifedipine was 18 days, and in seven patients no problems were encountered.

Our experience suggests that combining β-blockers with nifedipine in pregnancy is effective in controlling blood pressure. It is not possible, however, to rule out the possibility of detrimental effects on the fetus, and when considered with the results in sheep, we believe that this combination should only be used in severe hypertension, or in the context of a controlled trial, for the present time.

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Received 22 December 1986
Accepted 29 April 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1143–1149

Whole blood viscosity during normal pregnancy

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Summary. In a serial study the changes in whole blood viscosity at different shear rates and its major determinants were determined in 24 healthy women with normal pregnancies. Whole blood viscosity and plasma viscosity were measured with a rotational viscometer. Red cell aggregation was measured by syllectometry. During normal pregnancy we found a decrease in whole blood viscosity at all shear rates until 29 weeks gestation, followed by a smaller increase between 30 and 37 weeks, which was most pronounced at higher shear rates, especially in nulliparae. The changes in whole blood viscosity were to a great extent determined by the changes in haematocrit and plasma viscosity. Haematocrit was more important for whole blood viscosity at lower shear rates, while plasma viscosity had more influence on high shear blood viscosity. The continuous increase in red cell aggregation had no demonstrable influence on low shear blood viscosity as measured *in vitro* in a rotational viscometer.

The rheological properties of human blood are mainly determined by the concentrations of red cells and the various plasma proteins, by the red cell aggregation and by the red cell deformability. The resultant of these factors is the whole blood viscosity, which is in a non-linear way dependent on the shear rate: at lower shear rates red cell aggregation occurs, which is responsible for a progressive increase in whole blood viscosity. Normally, lower shear rates are found in the venules and small veins. The intervillous space of the human placenta is thought to resemble an area with lower shear rates (Schmid-Schönbein 1984). To obtain useful information about whole blood viscosity *in vivo*, viscometric measurements, covering the whole range of shear rates occurring in the vascular system, are therefore required.

During pregnancy the composition of maternal blood changes dramatically. The changes include a decrease in red cell concentration and an increase in fibrinogen concentration. In general, haemodilution reduces whole blood viscosity, whereas a rise in fibrinogen concentration enhances red cell aggregation, thereby increasing whole blood viscosity at lower shear rates. In spite of the haemodilution during normal pregnancy we found a considerable increase in red cell aggregation, which was mainly attributed to the increase in fibrinogen concentration (Huisman *et al.* 1987*a*). Moreover, the continuous rise in fibrinogen concentration during pregnancy was responsible for a significantly increased plasma viscosity near term (Huisman *et al.* 1987b).

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Only two studies have been published dealing with changes in whole blood viscosity during normal pregnancy, based on serial measurements (Inglis *et al.* 1982; Buchan 1984) Neither of these studies presents red cell aggregation measurements. Inglis *et al.* (1982) give only data on whole blood viscosity calculated at a standard haematocrit of 45%. Buchan (1984) measured whole blood viscosity at one shear stress.

Regarding the haemorheological changes during pathological pregnancies, several cross-sectional studies have been published. Some investigators reported higher whole blood viscosity values in pregnancies complicated by pre-eclampsia (Heilmann *et al.* 1977; Hobbs *et al.* 1982; Buchan 1982; Thorburn *et al.* 1982; Lang *et al.* 1984) or intrauterine growth retardation (Thorburn *et al.* 1982; Lang *et al.* 1984; Zondervan *et al.* 1985), whereas others did not find differences between patients with pre-eclampsia and a matched control group (Inglis *et al.* 1982). The higher whole blood viscosity values in patients with pre-eclampsia and/or intrauterine growth retardation have been attributed to a high red cell concentration (Buchan 1982; Lang *et al.* 1984), a raised fibrinogen concentration (Hobbs *et al.* 1982), a reduced red cell deformability (Thorburn *et al.* 1982; Lang *et al.* 1984), a raised plasma viscosity (Heilmann *et al.* 1977) and an enhanced red cell aggregation (Heilmann *et al.* 1977).

Understanding of the physiological changes in whole blood viscosity during pregnancy is a prerequisite for the interpretation of the changes in whole blood viscosity reported in pathological pregnancies. The present study was designed to investigate the changes in whole blood viscosity at various shear rates and to explore to what extent the major determinants contribute to these changes.

Patients and methods

Fourteen nulliparae and ten multiparae were studied during their uncomplicated pregnancy. During this or a previous pregnancy none had pregnancy-induced hypertension (PIH) or a low weight for gestational age infant (SGA) As a criterion for PIH we used a diastolic blood pressure rise of more than 15 mmHg above the first trimester value. SGA was defined as a birthweight below the 10th centile of the Dutch birthweight centiles (Kloosterman 1970). Supplemental iron was not prescribed during pregnancy. From the 32 pregnant women originally studied, eight had to be removed from the study group because of SGA ($n = 3$), PIH ($n = 2$), preterm delivery ($n = 1$), anaemia with low iron stores (serum ferritin below 10 µg/l, $n = 1$) and incomplete data ($n = 1$). So, we were left with 24 women who were delivered at term of appropriate-for-dates infants after uncomplicated pregnancies. Before the beginning of the study informed consent was obtained from all the women.

Blood was withdrawn from the cubital vein at 14, 22, 30 and 37 weeks gestation, and at 8 weeks postpartum. Because Buchan (1984) found no differences in haemorheological measures between non-pregnant women and women at 6 weeks postpartum, we used our 8 weeks postpartum values as non-pregnant values. All samples were collected between 09.00 and 10.30 hours. Blood was anticoagulated with EDTA. For the determination of the fibrinogen concentration according to Clauss (1957), we used citrate for anticoagulation. The haematocrit was measured with a Coulter S cell counter. Red cell aggregation was measured by syllectometry according to Brinkman *et al.* (1963). As a measure for the rate of red cell aggregation we used the aggregation half time. To exclude the influence of the red cell concentration, the aggregation half time was corrected to a haematocrit of 36% (Jansonius & Zijlstra 1965). During normal pregnancy this corrected aggregation half time is mainly determined by the fibrinogen concentration (Huisman *et al.* 1987*a*).

Whole blood viscosity and plasma viscosity were measured with a rotational viscometer (Contraves LS 30) at 37 °C. The standardization and automation of the measurement by means of a microcomputer has been described previously (Goslinga 1984). During transport from the hospital to the laboratory the blood samples were kept in motion in a cylinder, rotating at a velocity of 5 r/min. After arrival in the laboratory the blood samples were placed on a disc rotating in a water bath of 37 °C until the actual measurements in the viscometer were made. By keeping the blood samples thoroughly mixed until the measurement, it was possible to keep the coefficient of variation of the whole blood viscosity measurements below 5% during at least 6 h after blood sampling. All whole blood viscosity measurements were made between 4 and 5 h after the blood was obtained. Whole blood viscosity was measured at native haematocrit at ten different shear rates from 0·016 to 118·2 s^{-1}. As representative for whole blood viscosity at low shear rates (WBV-LS), at medium shear rates (WBV-MS) and at high shear rates (WBV-HS) we used the values at 0·04, 4·0 and 118·2 s^{-1}, respectively.

For statistical comparison of the data at the study periods during pregnancy and postpartum Wilcoxon's signed rank test for paired samples was used. To evaluate possible differences in changes between nulliparae and multiparae we used the Mann–Whitney test. As a nominal level of significance the value 0·05 was chosen. The influence of the variables on the resulting whole blood viscosity at different shear rates was evaluated by multiple regression analysis.

Results

The whole blood viscosity values at different shear rates and their determinants are given in Table 1 and Fig. 1. At all shear rates we found a significant decrease in whole blood viscosity up to 29 completed weeks, followed by a significant increase from 30 to 37 weeks. In comparison with the non-pregnant values, all pregnancy values of whole blood viscosity were significantly lower at all shear rates. At shear rates above 4·0 s^{-1}, nulliparae showed a significantly more pronounced increase in whole blood viscosity from 30 to 37 weeks.

The changes in plasma viscosity, fibrinogen concentration, (corrected) aggregation half time and haematocrit have been described elsewhere (Huisman *et al.* 1987*a,b*). After a slight decrease during the first trimester, plasma viscosity showed a statistically significant increase towards term, the value at 37 weeks exceeding the non-pregnant value. The fibrinogen concentration increased considerably during normal pregnancy. All values were significantly higher than the non-pregnant value. During pregnancy, red cell aggregation was enhanced, as indicated by a decrease in corrected aggregation half time. From 22 weeks onwards the pregnancy values were significantly lower than the non-pregnant value. With regard to the changes in haematocrit we found a decrease up to 29 weeks gestation, followed by a smaller increase from 30 to 37 weeks. Both changes were statistically significant. All pregnancy values were significantly lower than the non-pregnant values.

The influence of the independent variables plasma viscosity, haematocrit, corrected aggregation half time and parity on the whole blood viscosity at low, medium and high shear rate as the dependent variable was evaluated by multiple regression analysis. At all shear rates we found a significant regression coefficient on plasma viscosity and on haematocrit at all study periods during pregnancy (Table 2). The regression coefficients on plasma viscosity increased with the shear rate at which whole blood viscosity was measured, while the regression coefficients on haematocrit decreased with rising shear rates. On the variables corrected aggregation half time and parity we never found significant regression coefficients. The variables plasma viscosity and haematocrit together explained 52–76% of the whole blood viscosity at low shear rate, 65–89% of the whole blood

Table 1. Whole blood viscosity at low shear rate (WBV-LS, $\gamma = 0{\cdot}04\ \mathrm{s}^{-1}$), at medium shear rate (WBV-MS, $\gamma = 4{\cdot}0\ \mathrm{s}^{-1}$) and at high shear rate (WBV-HS, $\gamma = 118{\cdot}2\ \mathrm{s}^{-1}$), plasma viscosity (PV), fibrinogen concentration, corrected aggregation half time (AHT$_c$) and red cell volume (haematocrit) during pregnancy and at 8 weeks postpartum in 24 women with normal pregnancies

	Gestational age (weeks)									
Variable	14		22		30		37		Postpartum	
WBV-LS (mPa.s)	52·9	(7·5)	46·4	(6·3)	44·2	(5·5)	48·0	(7·9)	58·3*	(7·8)
WBV-MS (mPa.s)	7·64	(1·14)	7·07	(0·99)	6·84	(0·72)	7·54	(1·19)	8·65*	(1·15)
WBV-HS (mPa s)	3·54	(0·29)	3·41	(0·28)	3·36	(0·21)	3·55	(0·33)	3·79*	(0·27)
PV (mPa s)	1·28	(0·06)	1·29	(0·07)	1·30	(0·06)	1·34	(0·09)	1·30	(0·06)
Fibrinogen (g.l^{-1})	3·23	(0·57)	3·45	(0·52)	3·89	(0·41)	4·20	(0·72)	2·62*	(0·45)
AHT$_c$ (s)	5·2	(1·2)	4·9	(1·0)	3·9	(0·8)	3·4	(0·8)	6·0	(1·7)
Haematocrit (%)	38·8	(2·8)	36·8	(2·8)	36·0	(2·6)	37·2	(2·6)	41·1*	(3·0)

Results are mean (SD).
*Significantly different from all pregnancy values ($P<0{\cdot}05$)

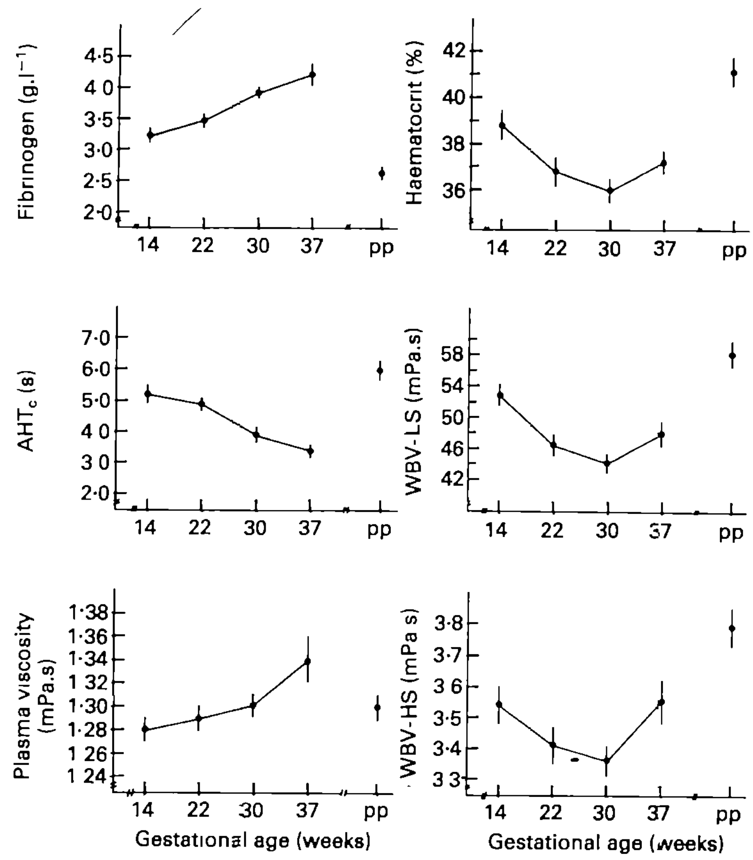

Fig. 1. Fibrinogen concentration, corrected aggregation half time (AHT$_c$), plasma viscosity, haematocrit, and whole blood viscosity at low and high shear rate (WBV-LS and WBV-HS) (mean±SEM) during pregnancy and at 8 weeks postpartum (pp) in 24 women with normal pregnancies

viscosity at medium shear rate and 66–76% of the whole blood viscosity at high shear rate.

Discussion

During normal pregnancy whole blood viscosity at all shear rates decreases up to 29 weeks gestation and increases from 30 to 37 weeks. This increase is more pronounced at higher shear rates. All pregnancy values were significantly lower in comparison with the non-pregnant value. The changes in whole blood viscosity were to a great extent determined by changes in plasma viscosity and haematocrit. Nulliparae and multiparae did not show significant differences in the changes of whole blood viscosity measured at low shear rates ($<4{\cdot}0\,s^{-1}$). However, the differences in the changes of whole blood viscosity at higher shear rates between 30 and 37 weeks reached the level of significance. As the impact of the various determinants of whole blood viscosity is highly dependent on the actual shear rate, the changes in whole blood viscosity and its major determinants will be discussed for the low and high shear rates separately.

The non-Newtonian behaviour of human blood at low shear rates, especially below $10\,s^{-1}$, is caused by red cell aggregation. During pregnancy we found a considerable increase in red cell aggregation, as indicated by the decrease in corrected aggregation half time. The changes in red cell aggregation were mainly determined by the changes in fibrinogen concentration (Huisman *et al.* 1987*a*). With regard to the whole blood viscosity at lower shear rates, this increase in red cell aggregation should counteract the decreasing influence of the fall in haematocrit up to 29 completed weeks. Between 30 and 37 weeks the influence of the changes in both determinants of low shear blood viscosity act in the same direction. However, the changes in whole

Table 2. Multiple regression equation ($Y = a+b_1X_1+b_2X_2$) of whole blood viscosity (Y) at low (WBV-LS), medium (WBV-MS) and high shear rate (WBV-HS) on the independent variables haematocrit (X_1) and plasma viscosity (X_2) and the corresponding percentage of explained variance (%) during pregnancy and at 8 weeks postpartum

	Gestation (weeks)	$Y = a+b_1X_1+b_2X_2$			Per cent
		a	b_1	b_2	
WBV-LS	14	−63	1·7**	39*	52
	22	−48	1·5**	31*	65
	30	−61	1·4**	42*	58
	37	−95	2·2**	46*	72
	pp	−55	2·2**	19	76
WBV-MS	14	−17·4	0·23**	12·6**	74
	22	−10·4	0·19**	8·2**	75
	30	−8·8	0·18**	7·1**	65
	37	−13·8	0·29**	8·0**	68
	pp	−14·4	0·28**	9·0**	89
WBV-HS	14	−2·9	0·050**	3·6**	73
	22	−1·3	0·040**	2·5**	66
	30	−1·7	0·040**	2·8**	71
	37	−2·2	0·062**	2·5**	66
	pp	−1·5	0·057**	2·3**	76

pp, Postpartum.
*P<0·05; **P<0·01.

blood viscosity at low shear rate closely follow the changes in haematocrit. We could not demonstrate any influence of the enhanced red cell aggregation. As shown by multiple regression analysis, whole blood viscosity at low shear rates in pregnancy is determined by plasma viscosity and haematocrit, but the haematocrit is the more important variable.

With increasing shear rate disaggregation occurs until at shear rates above $100\ \mathrm{s}^{-1}$ disaggregation is complete. Under these circumstances human blood behaves as a Newtonian fluid, with a linear relation between whole blood viscosity and haematocrit. In our study the rise in high shear whole blood viscosity exceeded the rise in haematocrit between 30 and 37 weeks in nulliparae. Most likely, this is the result of the sharp increase in plasma viscosity during this period, especially in nulliparae (Fig. 2). The importance of the plasma viscosity for the whole blood viscosity at high shear rates is also indicated by the results of the multiple regression analysis. The contribution of the plasma viscosity increased with increasing shear rate, while the contribution of haematocrit decreased.

We found the same pattern of changes in whole blood viscosity during pregnancy as Buchan (1984). Inglis *et al.* (1982) measured whole blood viscosity at low ($0{\cdot}2\ \mathrm{s}^{-1}$) and high shear rate ($128\ \mathrm{s}^{-1}$) and presented the results after correction to a standard haematocrit of 45%. Because normal pregnancy is characterized by a physiological haemodilution, this correction eliminated the effect of gestational age on whole blood viscosity. Surprisingly, they found a significant fall in corrected low shear viscosity between 12–16 and 26–32 weeks, whereas the fibrinogen concentration and the plasma viscosity both increased during the same period. Possibly, this fall is the result of the correction itself.

We did not correct our whole blood viscosity values for changes in haematocrit by means of a regression line based on the blood of many individuals (Inglis *et al.* 1981; Weaver *et al.* 1969). Inglis *et al.* (1981) pointed out the theoretical objections against such a correction. In our opinion, the only way to correct whole blood viscosity for haematocrit should be by a correction based on three or more measurements of the same blood at different haematocrit. Correction by means of regression lines, obtained by measuring whole blood viscosity in blood samples of different subjects with various haematocrits, neglects the changes in the other determinants of whole blood viscosity during normal pregnancy.

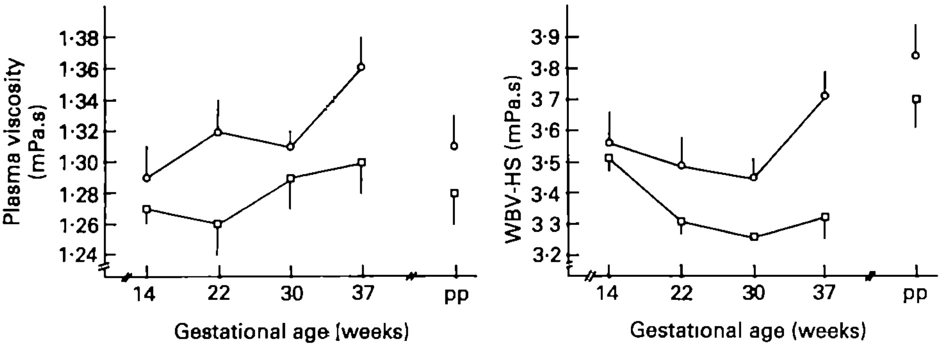

Fig. 2. Whole blood viscosity at high shear rate (WBV-HS) and plasma viscosity (mean±SEM) during pregnancy and at 8 weeks postpartum (pp) in 14 nulliparae (○) and 10 multiparae (□) with normal pregnancies

Red cell deformability was not measured in this study, because there was no generally accepted, reliable method. The lack of standardization of red cell deformability measurements makes comparison of the results of various studies difficult. A decrease in red cell deformability during normal pregnancy (Inglis *et al.* 1982), as well as an increase has been described (Thorburn *et al.* 1982). In another study an increase until 31 weeks, followed by a decrease until term was found (Buchan 1984). In all these investigations a microfiltration technique was used, either with washed red cells (Inglis *et al.* 1982) or with red cells resuspended in native plasma (Buchan 1984; Thorburn *et al.* 1982). Whether red cell deformability increases, decreases or remains unchanged during pregnancy, is still uncertain (Buchan 1984).

The fact that we could not demonstrate any influence of the increased red cell aggregation on the low shear whole blood viscosity, measured in a rotational viscometer, requires further comment. Our findings tally with observations by Schmid-Schönbein *et al.* (1976), who showed that it is difficult to demonstrate an enhanced red cell aggregation with a rotational viscometer. This is in apparent contradiction with the theory of the effective cell volume in which the increase in whole blood viscosity at shear rates below $10\,s^{-1}$ is attributed to an increase in effective haematocrit caused by the rouleaux formation of red cells in normal plasma (Chien 1970). Because part of the plasma volume is immobilized within the rouleaux, this results in an increase in effective haematocrit. However, the dense networks of red cell aggregates, caused by an increased red cell aggregation, do not immobilize more plasma than the loose discontinuous networks in human blood with a normal aggregation tendency. In other words, in normal human blood the aggregation phenomenon is already so pronounced, that an intensification is not reflected in an increase in effective haematocrit (Schmid-Schonbein 1976). Moreover, rotational viscometry underestimates the effect of red cell aggregation because of phase separation between red cell aggregates and plasma in the viscometer (Schmid-Schönbein *et al.* 1973). This raises the question as to the influence of the enhanced red cell aggregation of pregnancy on whole blood viscosity *in vivo*.

The intervillous space is a part of the circulation with low pressure gradients and probably very low shear rates. The blood flow in the intervillous space has been described as a creeping flow through a porous medium which is very suitable for red cell aggregation (Schmid-Schönbein 1984). The creeping flow around the villous obstacles is characterized by stop and go phenomena. To re-establish flow after a flow stop, the incident shear stress has to be higher than the yield shear stress, defined as the minimal shear stress to restore flow. The yield shear stress is determined by the haematocrit and the aggregation tendency of the red cells. With conventional rotational viscometers, the yield shear stress cannot be measured due to phase separation between red cell aggregates and the 'lubricating' plasma film in the viscometer (Schmid-Schonbein 1981). Therefore the yield shear stress is usually determined by extrapolation from viscosity measurements at higher shear rates assuming a linear relation between the square root of the shear rate and the square root of the shear stress, as originally suggested by Casson (Merill 1969). In our study the yield shear stress decreased from an average non-pregnant value of 7·1 mPa to 3·9 mPa at 30 weeks, thereafter slightly increasing to 4·9 mPa at 37 weeks. Thus, in spite of the increased red cell aggregation the yield shear stress decreased during pregnancy, mainly as a result of the decrease in haematocrit up to the 30th week. The dominating influence of the changes in haematocrit on the yield shear stress during pregnancy is in agreement with the in-vitro study by Kiesewetter *et al.* (1979). In our opinion, the decrease in haematocrit probably not only compensates for the enhanced red cell aggregation tendency, but more importantly, also diminishes the intervillous resistance to blood flow during normal pregnancy.

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Received 18 December 1986
Accepted 10 March 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1150–1155

Uterine artery blood velocities during contractions in pregnancy and labour related to intrauterine pressure

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Summary. Doppler recordings from branches of the uterine artery were made simultaneously with intrauterine pressure measurements in eight women in labour. Blood velocities fell and pulsatility index (PI) increased during all 22 contractions studied. Velocities were reduced almost linearly by up to 60% when pressure increased from 0 to 50 mmHg. To study the effect of uterine contractions before labour on uterine blood flow, simultaneous Doppler recordings from branches of the uterine artery and external tocodynamometry were made in seven women during the last trimester. Velocities fell during 18 of the 20 contractions studied (median 35%, range 19–71%). Extrapolating from labour contractions, this corresponds to a pressure increase of 30–40 mmHg. Fetal heart rate (FHR) recordings were normal during all contractions.

In an earlier study (Janbu *et al.* 1985) we described reduction in blood flow in uterine arteries during uterine contractions in labour. In the branches of the uterine artery, which can be found along the lateral uterine wall (Campbell *et al.* 1983), there was a median drop of 60% during normal uterine contractions in labour. The intrauterine pressure was not known because the contractions were monitored externally. Similar results were described by Fendel *et al.* 1984). A study in sheep (Greiss 1966) showed increasing reduction of blood flow (electromagnetic measurement) as intrauterine pressure rose during oxytocin stimulation. In the present study in women, blood velocities in the branches of the uterine artery have been correlated with simultaneous measurement of intrauterine pressure. We also describe the effect of contractions before labour on uterine blood velocities.

Patients and methods

Simultaneous Doppler and intrauterine pressure recordings were made in eight women (five were nulliparous and three had given birth once) in established first stage normally progressing labour with either spontaneously ruptured membranes or after amniotomy; all had normal pregnancies and were delivered at term, Seven were uneventful vaginal deliveries; one had a caesarean section because of late FHR decelerations. All babies were healthy with weights appropriate for gestational age (Bjerkedal *et al.* 1973). All labours started spontaneously, three were later stimulated with oxytocin. One woman had received an epidural block, the others N_2O and/or pethidine.

Seven other women with normal contractions before labour were studied with simultaneous Doppler and external tocodynamometry at between 1·5 days and 4 weeks (median 2 weeks) before the onset of labour. Six were nulliparous and one primiparous. Five had normal pregnancies with labour at term and an appropriate-for-

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gestational-age infant. One had pre-eclampsia (blood pressure 150/100); she was delivered 5 weeks prematurely by caesarean section because of increasing blood pressure and suspected fetal asphyxia. The infant weighed 2000 g (the 10th birthweight centile) with Apgar scores of 4 and 6 at 1 and 5 min. The last subject was delivered by caesarean section at term because of vaginal bleeding caused by a marginal placenta. The infant weighed 3330 g with Apgar scores of 8 and 9 at 1 and 5 min respectively.

The contractions were unselected in the sense that after a satisfactory Doppler signal was obtained, all contractions were accepted. All subjects were studied in the lateral recumbent position; all gave informed consent to the study.

Equipment

A pulsed Doppler (UNIDOP) (Wille 1977; Guldvog *et al.* 1980; Hatteland & Eriksen 1981) was used to obtain Doppler signals from branches of the uterine arteries. With a 1·5 MHz transducer the arteries were located by searching along the lateral wall of the uterus at a depth of 1·5–4·0 cm directing the ultrasound beam tangentially through the uterine wall. The signals were spectrum analysed (fast Fourier transform) every 10 ms (Pedersen 1982) and displayed on a screen in real time to ensure the measurement was from the whole cross-section of a branch of the uterine artery. Continuous recordings for up to 40 min were stored on tape together with ECG signals for later analysis by an ALTOS microcomputer. The time average of the instantaneous mean velocity during each cardiac cycle was calculated, estimating an angle of insonication of 45°. The ALTOS computer was also programmed to calculate the pulsatility index (PI) (maximal systolic–end diastolic velocity)/mean velocity (Gosling & King 1975).

Intrauterine pressure was measured in mmHg with a fibre-optic pressure transducer system (AE85, Camtech Ltd, Norway) (Svenningsen & Jensen 1986), in which light is transmitted through a fibre-optic bundle and reflected from a terminal pressure sensitive stainless steel membrane, protected by a dome with two side holes. The amount of light received by a separate detecting fibre bundle is dependent on the distance between the bundle and the reflecting membrane. This distance varies with the pressure applied. After inserting the transducer in the uterus, the fibre-optic system was connected to a Corometrics cardiotocograph. Intrauterine pressure in mmHg was continuously presented in real time.

Contractions before labour were recorded transabdominally by an external sensor connected to the cardiotocograph.

FHR was continuously recorded in all subjects, either transabdominally or, from subjects in labour, with a fetal scalp electrode.

Results

Blood velocities and PI were stable between contractions.

Contractions during labour

Twenty-two contractions were studied with maximal pressure increases from 25 to 70 mmHg. Blood velocities fell and PI increased during every contraction in all subjects. Figure 1 shows a continuous recording during 34 min from one woman.

Changes in Doppler spectra were first seen as reductions in diastole. Velocities started falling immediately the intrauterine pressure increased and continued to fall almost linearly until the velocity drop was approximately 60% at a pressure increase of 50 mmHg. Further increases in pressure resulted in only slight further velocity reductions. The median blood velocity reductions at increasing intrauterine pressures are listed in Table 1, which includes all 22 contractions. Figure 2 shows how pressure change during one typical contraction affects blood velocity and PI, respectively. The velocity spectra at different pressures during one contraction are illustrated in Fig. 3.

The relaxation of pressure was accompanied by a reversal of the changes in velocities and spectra following the same pattern as during pressure increase.

Contractions before labour

Twenty contractions were studied. During 18 of these, from all seven women, velocities were reduced and spectra changed in the same way as during labour. The median reduction was 35% (range 19–71%). This is illustrated in Fig. 4 showing three consecutive contractions in one healthy woman with corresponding velocity reductions and PI increases in a branch of the uterine artery. The recordings were made 2·5

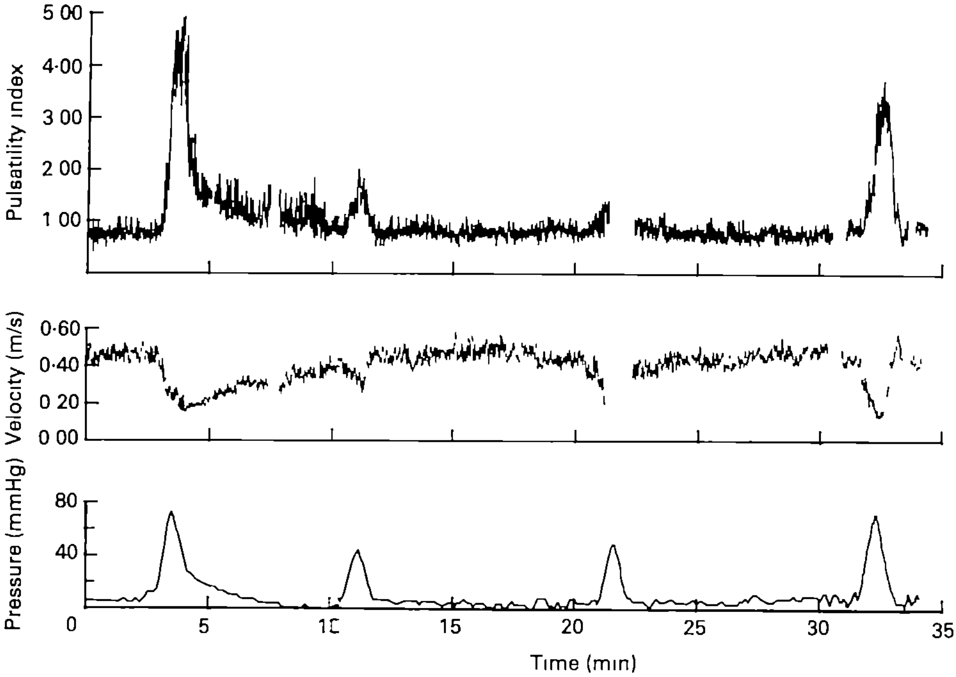

Fig. 1. PI (upper panel) and blood velocity (middle panel) in a branch of the uterine artery with simultaneous intrauterine pressure recording (lower panel) during 34 min including four labour contractions Doppler signal lost during third contraction

weeks before the uncomplicated birth of a healthy 3480 g infant at term. During the other two contractions (from two different women who also had contractions causing velocity reductions) no obvious changes in velocities or spectra were observed. No differences between the five normal and the two pathological pregnancies were noted.

FHR recordings were normal during all contractions.

Discussion

This is the first study in man where intrauterine pressure has been directly compared with reductions in uterine blood velocities.

If the examined artery could be displayed by a real time scanner during Doppler measurements, the angle between the sound beam and the vessel could be calculated. This is usually impossible because of the small dimensions and the tortuous course of the uterine branches traversing the myometrium. It is also difficult to distinguish the artery from the structure of the myometrium itself. The best linear array scanners would have a longitudinal resolution of typically 0·6 mm (with a 3·5 MHz transducer), and a lateral resolution of 3–4 mm at an optimal depth. This is about the diameter of the arteries of interest and makes them very difficult to detect.

By using an arbitrary set angle of 45° during calculations instead of presenting the Doppler data as frequencies (which are proportional to velocities), approximate values of the velocities are found. With a true angle of 65°, the velocity would be underestimated by 40%, with an angle of 25°, the velocity would be overestimated by 30%. The proportional velocity changes will be

Table 1. Velocity decrease, as a percentage of pre-contraction values, at increasing intrauterine pressures Twenty-two contractions from eight subjects are included

	Velocity decrease (%)	
Pressure increase (mmHg)	Median	Range
10	8	4–14
20	23	8–34
30	30	22–40
40	44	25–54
50	54	38–66
60	60	48–73

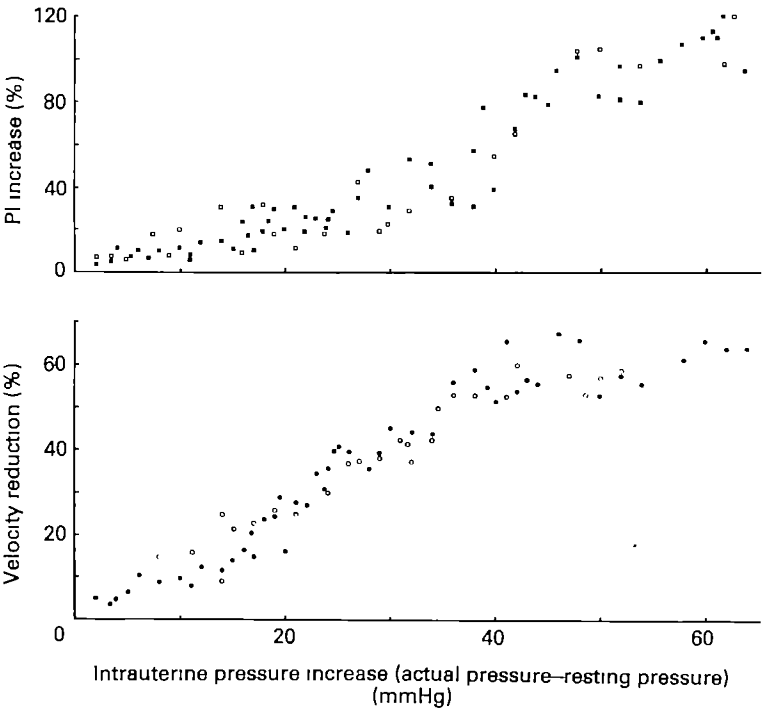

Fig. 2. PI changes (upper panel) and blood velocity changes (lower panel) during one labour contraction, as a percentage of the resting value. ■ ●, measurements during pressure increase; □ ○, measurements during pressure decrease.

correct, despite an inaccurate angle, as long as the angle is unchanged. This was ensured by not moving the Doppler transducer or changing the depth and is confirmed by the stable velocity found between contractions (Figs 1 & 4). In addition, PI, which is an angle-independent variable, was calculated.

By carefully directing the Doppler transducer almost tangentially through the lateral uterine wall and not moving it after a good signal is found, one is reasonably sure of studying a branch of the uterine artery. The normal Doppler spectrum has a characteristic recognizable shape with high end diastolic velocities and low pulsatility, different from other iliac branches (Taylor *et al.* 1985; Campbell *et al.* 1986). Continual real time display ensures the quality of the measurement.

Blood velocities in branches of the uterine artery are reduced almost linearly with intrauterine pressure increases from 0 to 50 mmHg. Considering the anatomy of the uterine arteries (Davidsohn 1893) one could be measuring either on branches just outside or traversing the myometrium. The latter vessels (possibly arcuate arteries) are likely to be increasingly compressed by the myometrium during a contraction, which would cause increased peripheral vascular resistance in vessels outside the myometrium. In the traversing branches increased arteriolar pressure would be expected, as a consequence of both increased venous pressure and direct compression of small vessels. In both instances a velocity reduction mainly in diastole could be expected. Although a rise in PI during contractions was demonstrated, PI might not be the most suitable variable in this case since velocity reductions during contractions are not caused by an increased peripheral resistance alone.

A marked retardation of uteroplacental blood flow during contractions was found by Borell *et al.* (1965) using arteriographic techniques. Blood flow reductions during contractions have also been measured with an electromagnetic flowmeter in pregnant sheep (Assali *et al.* 1958) with reductions in diastole appearing first. When intrauterine pressure increased above 25 mmHg, blood flow was significantly reduced (Assali *et al.* 1961). No blood flow reduction was observed below 15 mmHg. This is in contrast to our observation that blood velocities decrease immediately the pressure increases.

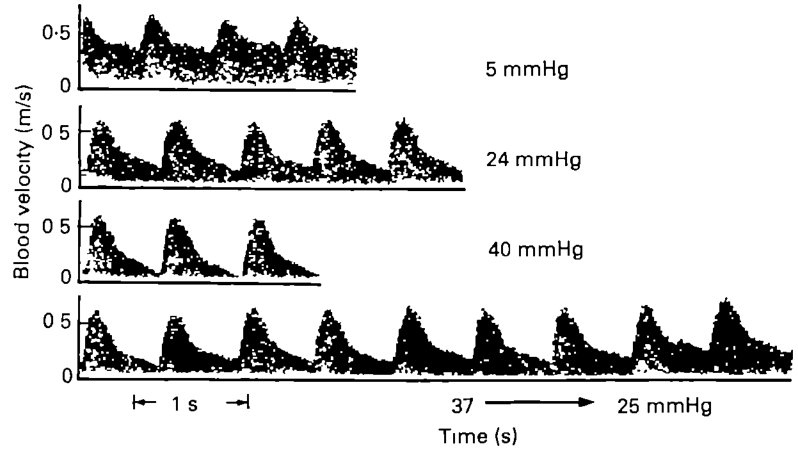

Fig. 3. Doppler spectra from a branch of the uterine artery in a woman in labour illustrating typical changes during one contraction. Upper panel between contractions (intrauterine pressure 5 mmHg); middle panels: spectra at 24 and 40 mmHg; lower panel: spectra during a fall in pressure from 37 to 25 mmHg

We found that blood velocities also declined during contractions before labour. This is in accordance with a more recent study on pregnant sheep (Sunderji *et al.* 1984) where a reduction in total uterine blood flow of 16% (diffusion technique) was found during contractions. No similar studies in man have been reported. As measurement of intrauterine pressure requires ruptured membranes, the pressure during contractions is unknown. Extrapolation from blood velocity changes during labour contractions indicates an intrauterine pressure increase of

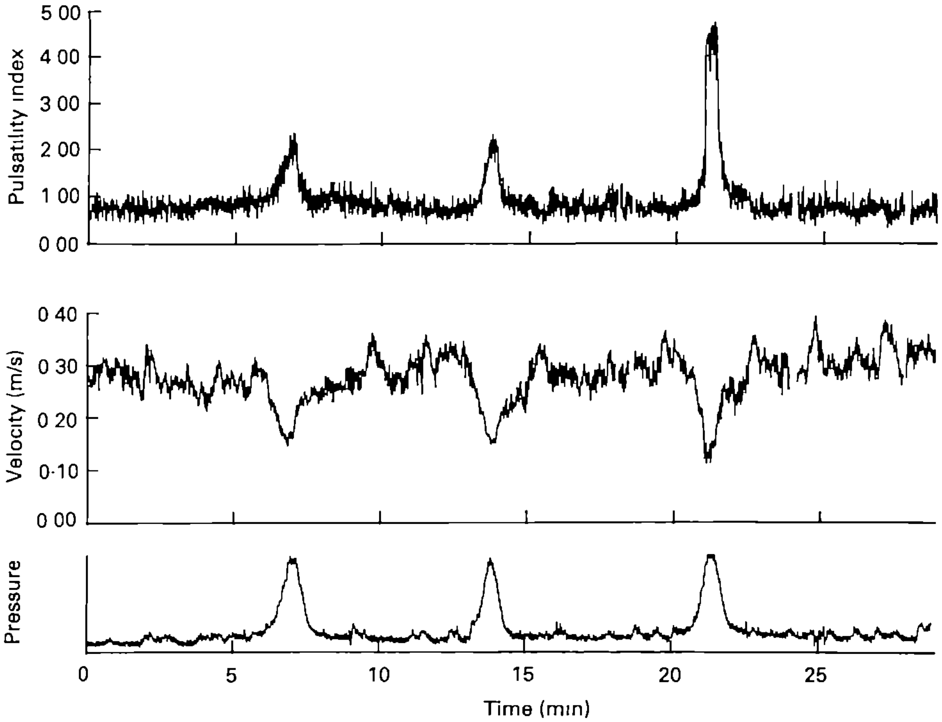

Fig. 4. PI (upper panel) and blood velocity (middle panel) in a branch of the uterine artery with external recording of simultaneous contractions (lower panel) from a healthy pregnant woman during 29 min including three contractions. Ordinate of lower panel. external contraction registration with arbitrary units.

approximately 30–40 mmHg during normal pregnancy contractions.

In a study in pregnant sheep, Brace & Brittingham (1986) showed FHR reductions during contractions. In another study in sheep, however, Skillman *et al.* (1985) showed FHR decelerations appearing only with reductions in uterine blood flow of more than 50% (electromagnetic flow measurement). Normally there are no changes in human FHR during contractions either before or in labour. This was the case in seven of the eight women studied during labour and in all seven pregnant women studied before labour. It must be concluded that the normal human fetoplacental unit is perfused with sufficient excess to protect the fetus during contractions lasting for 2–3 min which reduce perfusion up to 50–70%.

Acknowledgments

We thank Lars Walløe for valuable discussions. T. Janbu was supported by The Norwegian Research Council for Science and the Humanities. The development of the equipment was supported by Vingmed A/S, Oslo.

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Received 9 February 1987
Accepted 22 May 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol 94, pp. 1156–1158

Prostaglandins, chorioamnionitis and preterm labour

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Summary. The production of prostaglandin E (PGE) and leukotriene B_4 (LTB_4) by amnion was measured *in vitro* in 12 women delivered after spontaneous preterm labour and in 15 women delivered after spontaneous labour at term. The placenta and fetal membranes were examined histologically in all cases. PGE output (fmol/mg dry weight/2 h) in the amnions from uncomplicated preterm deliveries was low (median 486, range 232–3203, $n = 7$) compared with the values obtained after spontaneous labour at term (5529, 1722–14 226, $n = 15$). In amnions from preterm deliveries complicated by acute chorioamnionitis or round cell infiltration there was massive release of PGE (15 262, 10 905–27 640, $n = 5$) which was accompanied by an increase in LTB_4 production. Inflammatory infiltration of the fetal membranes results in a huge increase in PG production which could cause preterm labour.

Preterm labour is a major cause of perinatal mortality and morbidity, but in many cases its aetiology remains obscure. Increased prostaglandin (PG) production by the fetal membranes is believed to be associated with the spontaneous onset of labour (Casey & MacDonald 1986), but the factors controlling PG production in these tissues are not fully understood. Previous work (Bejar *et al.* 1981; Minkoff 1983) has underlined the importance of infection as a possible causative factor in preterm labour, and it has been demonstrated that bacterial products stimulate PGE production by cells from human amnion (Lamont *et al.* 1985). In the present study we have investigated the influence of chorioamnionitis on PGE production by amnion obtained from women after spontaneous preterm labour and delivery, and in comparison with findings after full term spontaneous labour and delivery. Furthermore, we have estimated the output of leukotriene B_4 (LTB_4) by the same tissues, in view of the increased release of this compound in inflammatory reactions (Lewis & Austen 1984).

Materials and methods

Placentas and fetal membranes were obtained from 12 women in whom spontaneous preterm labour led to delivery between 24 and 35 weeks gestation and in 15 women who had normal deliveries at term. The tissues were examined histologically in all cases (J.W.K.). Blocks of placenta were taken to include both fetal and maternal surfaces; samples of fetal membranes were obtained from the peripheral part of the sac; and a length of umbilical cord was taken from the placental end. The tissues were examined for polymorphonuclear leucocyte infiltration, other cellular infiltrates and evidence of inflammation. Histological examination was performed without knowledge of the laboratory estimations Discs of amnion were incubated in

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pseudoamniotic fluid (Schwartz *et al.* 1977) at 37°C for 2 h, and PGE and LTB_4 were estimated by radioimmunoassay (Mitchell & Flint 1978, and Amersham International, respectively) after extraction of the incubation medium on a solid reverse phase system (J. T. Baker Chemical Co.). Assays were performed without knowledge of the histology. In seven preterm deliveries histology was normal and the median gestational age was 32 (range 24–35) weeks. In the remaining five preterm deliveries, there was evidence of inflammatory infiltration in the placenta and/or membranes and the median gestational age was 26 (range 25–35) weeks. In four of them the tissues showed severe acute leucocytic infiltration, suggesting recent ascending infection; in one there was increased infiltration with round cells and macrophages, indicating previous infection or haemorrhage. These five cases are referred to as the chorioamnionitis group. There was no evidence of chorioamnionitis in the group delivered at full term. Statistical differences were assessed with the Mann–Whitney test.

Results

The median (range) PGE output (fmol/mg dry weight) in the amnions from uncomplicated preterm deliveries was 486 (232–3203) while in the chorioamnionitis group it was 15 262 (10 905–27 640) (Fig. 1). Chorioamnionitis was therefore associated with a massive increase in amniotic PGE production ($P<0{\cdot}01$). But in the absence of chorioamnionitis PGE production by amnions from spontaneous preterm labour was significantly lower ($P<0{\cdot}01$) than after spontaneous labour at term (median 5529, range 1722–14 226, $n = 15$). LTB_4 was produced by all amnions in the chorioamnionitis group and the median value was 820 (range 380–1370) fmol/mg dry weight (Fig. 1); in the absence of chorioamnionitis LTB_4 output was below 60 fmol/mg dry weight.

Discussion

These findings confirm that, in uncomplicated pregnancies, the PG synthesizing capacity of human amnion increases towards term (López Bernal *et al.* 1987). However, chorioamnionitis provokes a 30-fold increase in amniotic PGE production and this may cause the premature onset of labour. Our results help to explain the elevated PG levels found in amniotic fluid from women with intrauterine infection (Romero *et al.* 1986), but the reason for the increased PG production in the presence of inflammatory infiltration has not been established. It could be a response to bacterial factors (Lamont *et al.* 1985), a host-cell effect mediated by interleukin-1 (Romero *et al.* 1986) or other synergistic effects between amniotic and inflammatory cells. The accompanying increase in LTB_4 output confirms the presence of inflammatory reaction (Lewis & Austen 1984) and suggests that in chorioamnionitis there is an activation of both cyclo-oxygenase and lipo-oxygenase pathways; it would be of interest to examine the relative contribution of amniotic and inflammatory cells to each pathway.

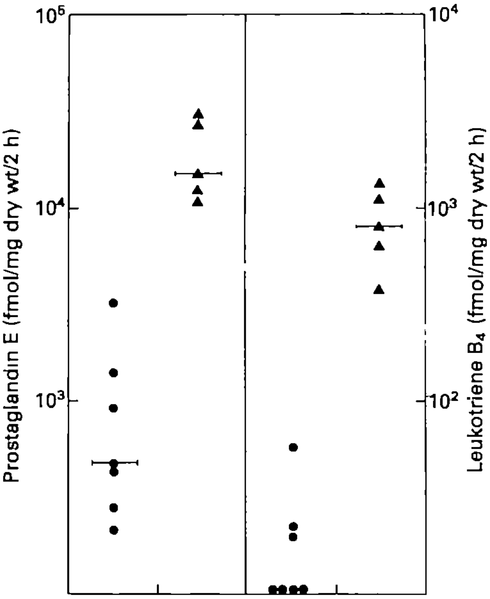

Fig. 1. Prostaglandin E and leukotriene B_4 production by amnion after spontaneous preterm labour The bars represent median values ●, Uncomplicated; ▲, chorioamnionitis

The incidence of chorioamnionitis in preterm deliveries in Oxford is about 30% (Zaaijman *et al.* 1982) and is usually a consequence of prolonged premature rupture of the membranes. While our results suggest how chorioamnionitis could cause preterm labour, there is no evidence of infection or haemorrhage in most spontaneous preterm labours where amniotic PGE production is low. The search for alternative mechanisms must continue.

Acknowledgments

Supported by Action Research, the National Fund for Research into Crippling Diseases, and by Sterling-Winthrop. The PGE antiserum was a gift from Dr M. T. Withnall, May & Baker Ltd.

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Received 19 February 1987
Accepted 14 April 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp 1159–1164

Is C-reactive protein really useful in preterm premature rupture of the membranes?

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Summary. In a prospective blind study 380 daily serum samples from 55 women with preterm premature rupture of the membranes were analysed for C-reactive protein (CRP). Although the last CRP before delivery was higher in patients with histological chorioamnionitis ($P = 0{\cdot}007$), considerable overlap between infected and non-infected pregnancies occurred, precluding the use of CRP as a diagnostic test if published normal levels were used. When upper limits were set at 30, 35, or 40 mg/l, the last CRP before delivery proved 90, 95 and 100% specific and 88, 92 and 100% positively predictive of infection in singleton pregnancies. Such high specificities are needed to prevent inappropriate intervention based on false positive results. We therefore propose upper limits for single estimations of 30, 35, or 40 mg/l depending on the relative risks of preterm delivery versus infection at various gestational ages. In addition, consecutive values >20 mg/l appeared highly predictive of infection.

Conservative management has been increasingly employed in preterm premature rupture of the membranes (PPROM), following the recognition that perinatal deaths from prematurity exceed those from infection (Schreiber & Benedetti 1980; Daikoku *et al.* 1981). Patients under expectant regimens, however, need frequent assessment for evidence of amnionitis, so that timely delivery may prevent morbidity arising from infection in both mother and infant (Johnson *et al.* 1981).

Unfortunately, clinical signs of intrauterine infection occur as late manifestations, while standard laboratory measurements of erythrocyte sedimentation rate, white blood count and differential are of limited use, being variably affected by pregnancy, labour and glucocorticoid administration (Gibbs 1977). An elevated C-reactive protein (CRP) has been suggested as an early indicator of infection in PPROM (Evans *et al.* 1980), but agreement is lacking on its precise role as a diagnostic test The initial report by Evans *et al.* (1980) found CRP to be highly specific rather than sensitive, while from the same institution, Ismail *et al.* (1985) reported the converse. Two centres reported both sensitivities and specificities to be high (Hawrylyshyn *et al*

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1983; Romem & Artal 1984), whereas Farb *et al.* (1983) found CRP lacking in both and cautioned against its use as a pathognomonic test. These diverse conclusions are explained in part by the different cut-off levels employed, which ranged from 12·5 to 20 mg/l.

This study was undertaken to ascertain the CRP level above which the test becomes highly predictive of infection.

Patients and methods

Patients admitted to the King George V Hospital, between March 1985 and June 1986 at 26–36 weeks gestation with ruptured membranes, confirmed by demonstration of pooling of amniotic fluid in the posterior fornix, were enrolled in the study. Only those in whom conservative expectant management was indicated were included. Patients with clinical signs of infection on admission were excluded, as were those with a history of chronic inflammatory conditions.

The project was conducted with the approval of the Royal Prince Alfred Hospital Ethics Committee, and 60 women gave written informed consent. Venepuncture for CRP, white cell count, differential and film was performed daily throughout latency.

CRP was measured by rate nephelometry (Beckman Instruments Inc., Fullerton, California), using a single point calibration based on purified CRP and monospecific antisera (Quantimetric 2, Kallestad, Austin, Texas). A value was not assigned to measurements below 6 mg/l. CRP results were unavailable to the investigators or clinicians involved until after discharge.

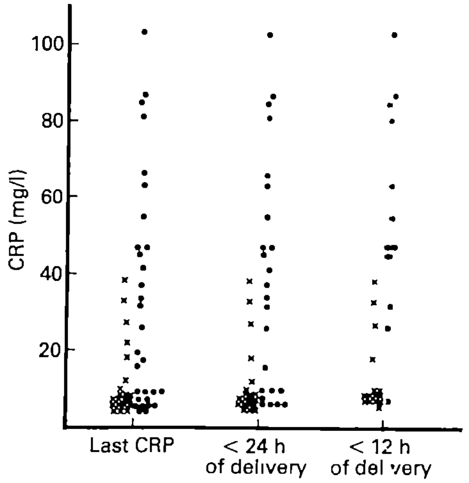

Fig. 1. Last C-reactive protein (CRP) value before delivery in singleton pregnancies with infected (●) and non-infected (×) placentas, overall ($P = 0{\cdot}007$), and for samples collected within 24 h ($P = 0{\cdot}002$) and 12 h ($P = 0{\cdot}0004$) of delivery

Patients developing non-obstetric infections were excluded from the study, as were those prescribed antibiotics during latency. Midstream urine samples were collected weekly for culture, and patients were asked daily about symptoms of respiratory and other non-genital infections.

Five patients were withdrawn: antibiotics were used in two, one declined further venepuncture, one was discharged after amniotic fluid drainage ceased for 7 days, and another developed a respiratory tract infection. Thus the final study population comprised 51 women with singleton pregnancies and four with twin pregnancies.

Management was at the discretion of the attending physician and usually included betamethasone administration at gestations <34 weeks and tocolysis with oral or parenteral salbutamol, if required, at gestations <32 weeks.

Clinical amnionitis was defined as the triad of uterine tenderness, purulent amniotic fluid, and maximum temperature ≥37·5°C in the preceding 24 h. These signs were sought daily during latency, and at the onset of labour. Maternal temperature was recorded every 4 h. The endpoint for infection in the study, however, was histological acute diffuse chorioamnionitis. This was assessed by one of two perinatal pathologists, using a membrane roll technique to examine a thin strip of membranes from the placental edge to the site of rupture (Benirschke 1961). Focal inflammation confined to the site of membrane rupture was not considered an infective phenomenon, as such change may represent a chemical response to amniorrhexis (Russell 1979).

Significance testing for the non-normally distributed CRP values was performed using the Mann–Whitney *U*-test, with the help of a Minitab package (Statistics Department, Pennsylvania State University).

Results

Histological examination of the placentas from 51 singleton pregnancies demonstrated acute diffuse chorioamnionitis in 30 and no evidence of infection in the remaining 21 (including six with focal inflammation at the site of membrane rupture). Figure 1 shows the last CRP value during latency in both groups as a function of time from delivery. In 44 women the last CRP was taken within 24 h of delivery and in 27 of them blood was obtained within 12 h of delivery. As blood was not collected during labour, seven patients had their last value taken 24–48 h before delivery.

Last CRP values were significantly higher in infected pregnancies both overall ($P = 0{\cdot}007$) and for estimations within 24 ($P = 0{\cdot}002$) and 12 h of delivery ($P = 0{\cdot}0004$). CRP was only 50% sensitive and 81% specific for histological infection, if 20 mg/l was used as the upper limit of normal. High specificities and positive predictive values were achieved only when cut-off values were set at 30, 35 or 40 mg/l (Table 1). Low sensitivities (37–47%) at these higher levels were considerably improved (75–83%) by including only values obtained within 12 h of delivery (Table 2).

All 11 patients with the last CRP value >40 mg/l had histological chorioamnionitis. None had the triad of clinical amnionitis at the time of blood collection, although five had one of the three signs. Two of these five and three others with CRP values >40 mg/l subsequently underwent intervention (induction or caesarean section) for clinical signs of infection. Ten patients overall underwent intervention for one or two signs of clinical amnionitis, one of whom proved to be non-infected on histological examination. The two patients in whom these signs were detected at the time of last blood collection had CRP values of 25 and 38 mg/l.

CRP elevation often preceded delivery or clinical infection by several days (Fig. 2). Thirteen of 14 patients with two daily estimations >20 mg/l, and 12 of 13 with consecutive estimations >20 mg/l had histological chorioamnionitis. Other than those values shown in Fig 2, no patient with a non-infected placenta had any CRP value >20 mg/l, despite latent periods of up to 23 days.

Triple vessel vasculitis was present in 14 of 26 singleton cords examined from infected placentas, of which only six were associated with CRP values >40 mg/l. Similarly, there were four patients with such values in the eight with infected placentas and inflammatory funisitis in two or fewer cord vessels.

White cell count, neutrophil count and blood film did not correlate with chorioamnionitis. Glucocorticoid administration in 39 patients produced variable degrees of left shift, while toxic granulation was evident in the film of two patients with non-infected and seven with infected placentas, in two of whom it disappeared before delivery.

Fifteen daily CRP estimations were performed in four patients with dichorionic twin pregnancies. The sac with ruptured membranes showed evidence of infection in three pregnancies, in all of them the second placenta was normal (Table 3). The last CRP was elevated (97 mg/l) only in one patient. In labour this woman developed group B streptococcal septicaemia.

Table 1. Accuracy of varying degrees of C-reactive protein (CRP) elevation in singleton pregnancies as a predictor of chorioamnionitis

	CRP cut-off value (mg/l)			
	>20	30	35	40
Sensitivity (%)	50	47	40	37
Specificity (%)	81	90	95	100
Positive predictive value (%)	79	88	92	100
Negative predictive value (%)	53	54	53	53

Table 2. Accuracy of varying degrees of C-reactive protein (CRP) elevation for values obtained within 12 h of delivery as a predictor of chorioamnionitis in singleton pregnancies

	CRP cut-off value (mg/l)			
	>20	30	35	40
Sensitivity (%)	92	83	75	75
Specificity (%)	73	87	93	100
Positive predictive value (%)	73	83	90	100
Negative predictive value (%)	92	87	82	83

Four women developed postpartum infectious morbidity—all with endomyometritis (temperature ≥38° on two occasions, plus local signs). Although 20 of 59 infants were colonized, only four (6·7%) developed an infective illness within the first 48 h, three with bacteraemia and one with pneumonia. Prophylactic antibictics were administered in 27.

Discussion

This prospective blind study confirms a significant association between elevated C-reactive protein and histological chorioamnionitis in PPROM. The pattern of CRP distribution in PPROM appears similar to that in other infective conditions (Pepys 1981) in that, although an association exists, its usefulness as a diganostic test is limited by overlap between infected and non-infected groups. This is reflected in a sensitivity of 50% and specificity of 81%, if 20 mg/l is used as the discriminator most commonly suggested.

The varying accuracies for CRP in the literature are largely explained by both the different indices of infection, i.e. clinical or histological and the various cut-off levels employed in those studies (Table 4).

Histological chorioamnionitis was chosen as the marker of infection in the study as clinical amnionitis is considered inaccurate. Indeed, 1 of 10 patients in this series and 2 of 18 in another (Ismail *et al.* 1985) allegedly developed clinical amnionitis, yet histology proved negative. Of our patients 60% had chorioamnionitis, in keeping with the 60–65% of previous studies (Hawrylyshyn *et al.* 1983; Ismail *et al.* 1985).

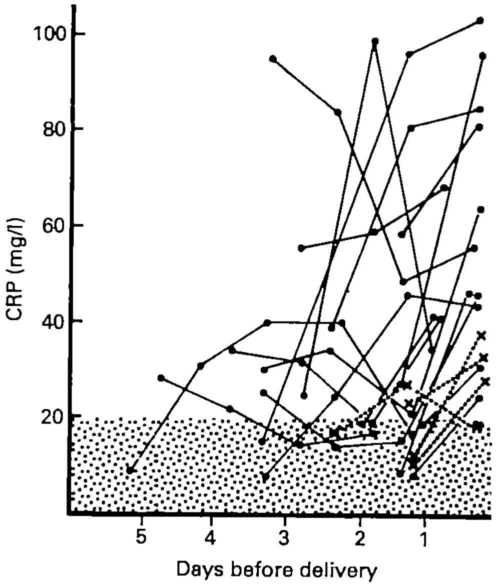

Fig. 2. Serial C-reactive protein (CRP) estimations in singleton pregnancies in the last week before delivery for those patients with any value >20 mg/l Single estimations due to short latency not shown. ●, infected; ×, non-infected.

Table 3. Placental histopathology and last C-reactive protein (CRP) estimation in four twin pregnancies

Patient	Placenta 1	Placenta 2	Last CRP (mg/l)
1	Chorioamnionitis	Normal	97
2	Chorioamnionitis	Normal	9
3	Chorioamnionitis	Normal	8
4	Normal	Normal	9

Table 4. Previous studies of C-reactive protein (CRP) as a predictor of infection in preterm premature rupture of the membranes (PPROM)

Reference	No studied	CRP cut-off (mg/l)	Outcome	Sensitivity	Specificity
Evans *et al.* (1980)	36	20	Infectious morbidity	80%	100%
Hawrylyshyn *et al* (1983)	32	12·5	Histological chorioamnionitis	88%	96%
Farb *et al* (1983)	31	20	Clinical amnionitis	56%	73%
	31	20	Histological chorioamnionitis	80%	68%
Romem & Artal (1984)	51	17·8–18·9*	Clinical amnionitis	86%	97%
Ismail *et al* (1985)	100	20	Clinical amnionitis	82%	55%
	100	20	Histological chorioamnionitis	67%	81%

* Varied with gestational age.

Evans *et al.* (1980) used an arbitrarily chosen upper limit of 20 mg/l to distinguish those with 'infectious morbidity' on histological or clinical criteria from those without ($P<0\cdot001$). Their lack of false positives was confirmed by the high specificities and positive predictive values, both 96%, of Hawrylyshyn *et al.* (1983), who used a cut-off level of 12·5 mg/l, predetermined in controls (Table 4). The only negative trial (Farb *et al.* 1983), whose conclusions have been criticized (Verma *et al.* 1984), analysed only 31 women with PPROM to report a poor association with clinical amnionitis. Nevertheless, the association was somewhat closer with their incomplete histological examination. Ismail *et al.* (1985) using a value of 20 mg/l reported an 82% sensitivity with a lower specificity of 55% for loosely diagnosed clinical amnionitis, but higher specificity (81%) than sensitivity (67%) for histological infection. Romem & Artal (1984) used clinical amnionitis and their own 95% confidence limit in controls, which increased with gestation from 17·8 to 18·9 mg/l (Romem & Artal 1985), to derive high sensitivities and specificities (86% and 97% respectively).

A rise in CRP has been shown to precede infective changes in currently available clinical and laboratory indicators (Evans *et al.* 1980; Romem & Artal 1984) and to be superior to them in predicting infection (Hawrylyshyn *et al.* 1983; Romem & Artal 1984). In this study, 15 patients with histologically demonstrated chorioamnionitis did not have clinical amnionitis at the time of blood collection, but had CRP >20 mg/l. Although CRP may be superior to current indicators, its use is hampered by false positives. Since other manifestations of infection occur late, an elevation of CRP is likely to be the sole abnormal sign. As suggested by Farb *et al.* (1983), only when a test has 100% predictive values can it be applied confidently in the clinical setting. From our data, negative and positive predictive values cannot both approach this goal. However, by raising cut-off levels higher than previously suggested to 40 mg/l, an elevated CRP in this study proved 100% positively predictive and specific. Intervention could be based on these new limits in the confidence that it would not lead to the delivery of babies when the membranes showed no histological evidence of infection.

The low sensitivity thereby achieved (37%), was improved considerably to 75% by taking only those values collected within 12 h of delivery. The main difference between values collected at different time intervals before delivery (Fig. 1) lies in the number of infected pregnancies with values ≤20 mg/l. Overall 15 infected pregnancies had such low last CRP values. This number fell to nine for those collected within 24 h, while only one pregnancy had a value ≤20 mg/l collected within 12 h of delivery. In view of the rapid rate of CPR production, 8–12 h (Powell 1979; Shine *et al.* 1981), low values found more than 12 or 24 h before delivery may have occurred in pregnancies that were initially not infected but acquired infection after the last sample was obtained.

Slightly higher sensitivities may be achieved by lowering cut-off levels to 35 or 30 mg/l (Table 1). Specificities remain ≥90% and the occasional false positive may prove acceptable at later gestations such as 34–36 weeks.

Due to small numbers, the wide confidence intervals of CRP accuracies in this and other studies must be acknowledged. For example, the 50% sensitivity and 81% specificity with 20 mg/l as the discriminator have approximately 95% confidence intervals of 32–68% and 64–98% respectively. Furthermore, specificities might be expected to be lower if CRP was used prospectively as a diagnostic test for infection leading to intervention.

Given the high frequency of histological chorioamnionitis and the low frequency of neonatal sepsis in PPROM series, the degree of histological cord inflammation has been suggested to predict more accurately the risk of infection to the newborn (Bader *et al.* 1975). We found no association between CRP elevation and the number of cord vessels involved. This is not surprising in that CRP, an acute phase reactant of hepatic origin, reflects only the degree of maternal response to inflammation.

From the small number of twins studied, CRP did not seem as useful. Two pregnancies with histological infection had low CRP values (9 and 8 mg/l), whilst one with infection had values of 90 and 97 mg/l, in the absence of clinical signs, in the 2 days before delivery.

The accuracy of CRP using the proposed cut-off levels compares favourably with a sensitivity of 55% and positive predictive value of 50% obtained with amniotic fluid culture (Feinstein *et al.* 1986). Collection of amniotic fluid, moreover, necessitates amniocentesis, which is only successful in up to 80% of patients with PPROM (Fisk 1987; Broekhuizen *et al.* 1985), whereas blood for CRP is obtainable in all. Another promising predictor of infection, the absence of fetal breathing movements on ultrasound, has a higher sensitivity, 92% in a recent report (Vintzileos *et al* 1986), but its clinical usefulness is limited by a low positive predictive value of 50%

Further studies are needed to determine the merits of estimating CRP at more frequent intervals, for example every 12 h, and to assess the effect on maternal and neonatal infectious morbidity of intervention based on the elevated CRP levels proposed in this study.

If such a test is to achieve a place in the routine management of patients with PPROM, it is important to comment on the cost of the assay. The capital cost of an automated nephalometer is high, approximately A$ 40 000, although it has far wider use than just CRP and is standard equipment in most laboratories measuring proteins. The cost per test is <A$2 for reagents and US$7 for operator time for a run of up to 40 tests. Providing a reasonable workload is maintained, this is an inexpensive investigation, particularly if compared to costs of avoidable obstetric and neonatal care.

Acknowledgments

The authors wish to thank Dr P. Russell for his assistance and advice with placental pathology, and the staff of the Clinical Immunology Laboratory, Royal Prince Alfred Hospital, for performing the CRP assays.

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Received 4 February 1987
Accepted 15 June 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1165–1169

Production of prostacyclin, 6-keto-PGF$_{1\alpha}$ and thromboxane B$_2$ by human umbilical vessels increases from the placenta towards the fetus

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Summary. The aim of this study was to investigate the production of prostacyclin (PGI$_2$) and thromboxane B$_2$ (TXB$_2$) by incubated samples of umbilical arteries and veins taken at different distances (2,10,20,30 cm) from the placenta to provide additional information relevant to the haemodynamics of umbilical blood flow. The production of PGI$_2$, and 6-keto-PGF$_{1\alpha}$ (the stable metabolite of PGI$_2$), was higher in both veins and arteries as the distance from the placenta at which the vessels were sampled was increased. A similar correlation between production by venous rings and distance from the placenta was observed for TXB$_2$, but there was no apparent gradient of TXB$_2$ production by the samples of arterial rings. No statistically significant variations were discernible in the ratio of 6-keto-PGF$_{1\alpha}$:TXB$_2$ (~50 in the veins and ~20 in the arteries) in relation to the sampling distance. The significance of these high ratios is discussed in relation to umbilical blood flow and fetal well-being and development.

The factors that regulate blood flow in the umbilical vessels are not known in detail, but some experimental data suggest that prostacyclin (PGI$_2$) and thromboxane A$_2$ (TXA$_2$) may have opposing biological effects in the control of the umbilical circulation (Benedetto *et al.* 1985*b*; Kawano & Mori 1983; Makila *et al.* 1983; Tuvemo 1980). It has been demonstrated that both umbilical veins and arteries produce substantial amounts of PGI$_2$, and much lower amounts of thromboxane B$_2$ (TXB$_2$) (Benedetto *et al.* 1985*b*). Moreover, in spite of the close juxtaposition of the placental and umbilical blood vessels, it has been found that PGI$_2$-producing activity varies significantly between these two vascular compartments (Kawano & Mori 1983).

There is no published information on the production of TXB$_2$ at different distances along the umbilical cord. Furthermore, the data concerning the PGI$_2$-producing activity relate to limited regions of the umbilical vessels close to the placental junction (Kawano & Mori 1983).

The aim of this study was to investigate the production of PGI$_2$ and TXB$_2$ by incubated samples of umbilical arteries and veins taken at different distances from the placenta in order to provide additional information relevant to the haemodynamics of umbilical blood flow.

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Subjects and methods

The umbilical arteries and veins were obtained from the umbilical cords of 16 infants. Of the 16 mothers, 14 were primiparous; the mean age of the mothers was 26 (SD 6, range 18–38) years. The mean length of pregnancy was 39 (SD 1) weeks. Of the 16 women 4 were delivered by elective caesarean section. The means of the fetal and placental weights were 3146 (SD 534) g and 635 (SD 162) g. All the infants had Apgar scores of ≥8 at 1 min.

Preparation of samples

The preparation of platelet-rich (PRP) and platelet-poor (PPP) plasma and the induction of platelet aggregation by ADP (1μM, final concentration) were performed as described previously (Benedetto *et al.* 1985*b*).

The umbilical cords were taken immediately after the completion of the third stage of labour, or after the separation of the placenta during caesarean section, and put into Tris buffer (50 mM, pH 8) at 4°C for 10 min. Small samples of arteries and vein were isolated from each umbilical cord at distances 2, 10, 20 and 30 cm from the placenta and cut into fine rings (~8 mg wet weight) that were placed in fresh Tris buffer at 4°C for 5 min.

All of the rings from each sample, totalling 20–33 mg wet weight, were added to 200 μl of Tris buffer at room temperature and vortex-agitated for 15 s and then incubated at room temperature for 2 min, 45 s.

Samples (20 μl) of the supernatant solutions obtained from the above incubations were added to the PRP 1 min before the addition of ADP in order to measure the inhibitory effect on ADP-induced platelet aggregation (Moncada *et al.* 1977). The inhibition was compared with that of standard concentrations of PGI_2. The PGI_2-like activity in the supernatant solutions was checked for identity with PGI_2 by means of a specific antiserum to PGI_1 that cross-reacts with PGI_2 (Bunting *et al.* 1978).

6-keto-$PGF_{1\alpha}$ and TXB_2 were measured by radioimmunoassay (RIA) on duplicate samples of the same supernatants diluted 1:2 (TXB_2) and 1:20 (6-keto-$PGF_{1\alpha}$) in phosphate buffer (0·1 M, pH 7·4) containing 0·1% (w/v) sodium azide and 0·01% (w/v) bovine serum albumin, fraction V. The samples were hydrolysed by temporary acidification with 1 N HCl and allowed to stand at 37°C for 10 min, the pH being subsequently adjusted to pH 7·4 with 1 N NaOH before the RIA. The interassay-coefficients of variation for the 6-keto-$PGF_{1\alpha}$ and TXB_2 assays were 5% and 4% respectively. The lower limits of detection were approximately 2 pg/50 μl for 6-keto-$PGF_{1\alpha}$ and TXB_2.

Reagents

ADP and bovine serum albumin fraction V were obtained from Semmelweis s.r.l.-Mascia Brunelli (Milan, Italy) and Sigma Chemical Co. (Poole, UK) respectively. Tritiated 6-keto-$PGF_{1\alpha}$ and TXB_2 were purchased from Amersham International plc., UK.

6-keto-$PGF_{1\alpha}$ and TXB_2 standards were obtained from Upjohn Diagnostics (Kalamazoo, Michigan, USA). Antibodies to 6-keto-$PGF_{1\alpha}$, TXB_2 and PGI_1 were a generous gift from Dr J. Salmon (Wellcome Research Laboratories, Beckenham, UK). PGI_2 standard was kindly provided by Dr J. Pike (Upjohn Company, Kalamazoo, Michigan, USA).

Statistical analysis

Statistical analysis was performed on an IBM-370 computer using Biomedical Development Products (BMDP) Statistical Software (1985).

Given the assymmetrical distribution of concentrations and the corresponding increase of standard errors with the increase in mean values, a log transformation was applied in the analysis. To test for the main effect of grouping samples in arteries and veins, the effect of the distance from the placenta as well as variability between different subjects and their interactions, an analysis of variance (ANOVA) model for repeated measures was applied (BMDP2V). Because the symmetry assumption implied by standard ANOVA is unlikely to hold for a repeated-measures factor representing a time effect, or in this case the effect of different distances, an orthogonal polynomial decomposition was chosen. This was able to show that there is a linear trend in the measured concentrations, and that linear effects are a sufficient explanation for all distance effects. The orthogonal decomposition is used when the levels of the 'within-factor' (distance) are ordered but it assumes implicit equal spacing. To take into account the unequal distances from the placenta (2,10,20,30 cm) a POINT statement was included in the programme (Frane 1980). Linear regression and correlation were used to describe the linear trends so identified.

Results

The productions of PGI$_2$, 6-keto-PGF$_{1\alpha}$ and TXB$_2$ by samples of umbilical vessels isolated at different distances from the placenta are shown in Table 1.

PGI$_2$ and 6-keto-PGF$_{1\alpha}$-values

There was a marked trend in the production of PGI$_2$ (T-values, $P<0\cdot01$) and 6-keto-PGF$_{1\alpha}$ (T-values, $P<0\cdot0001$) by both veins and arteries as the distance from the placenta at which the vessels were sampled increased, and a linear trend was an adequate representation of the data (tests for trends of higher order were not significant).

The production of PGI$_2$ and 6-keto-PGF$_{1\alpha}$ was significantly higher in vein samples than in arteries (for the ratio, A/V, of the values from samples of arteries (A) to corresponding samples of veins (V), $P<0\cdot0001$).

The ratio between the production in vein and artery samples did not vary significantly with distance from the placenta, as shown by a not-significant interaction between the values for the artery and vein (I-values, Table 1) in the statistical analysis ($P = 0\cdot30$ and $P = 0\cdot90$ for interaction for PGI$_2$ and 6-keto-PGF$_{1\alpha}$ respectively).

TXB$_2$-values

The production of TXB$_2$ by samples of veins was greater as the distance from the placenta increased (T-values, $P<0\cdot0001$ for linear trend), but there was no apparent trend of TXB$_2$ production in the samples of artery rings.

The values obtained for the production of TXB$_2$ were not significantly different in veins compared with arteries (A/V-values, $P = 0\cdot59$) and were much lower than the corresponding values for 6-keto-PGF$_{1\alpha}$ both in veins and in arteries.

The ratio of TXB$_2$ production by veins compared with arteries also increased with distance from the placenta, ranging from 0·6 to 1·8 and this was confirmed by a significant interaction in the statistical analysis (I-values, $P<0\cdot02$ for interaction).

Ratio of 6-keto-PGF$_{1\alpha}$:TXB$_2$ values

The results demonstrate that neither vein nor artery samples showed a significant trend (T-values) for the ratio 6-keto-PGF$_{1\alpha}$/TXB$_2$ with increasing distance from the placenta ($P = 0\cdot61$) with a mean value of about 50 for veins and 20 for arteries. These mean values were significantly different (A/V-values, $P<0\cdot005$). No statistically significant changes in relation to the sampling distance were discernible in the ratio (I-values, Table 1).

The results obtained from the four umbilical cords obtained at caesarean section were not

Table 1. The contents of prostacyclin (PGI$_2$), 6-keto-PGF$_{1\alpha}$ and thromboxane B$_2$, (TXB$_2$), expressed as log (pg/mg of wet weight of the tissue), and the ratio of the original values of 6-keto-PGF$_{1\alpha}$:TXB$_2$ in the supernatant solutions obtained after incubating samples of 16 umbilical veins and arteries isolated at different distances from the placenta

Prostanoid	Samples of umbilical vessels	Distance from the placenta (cm)				Statistical analysis*		
		2	10	20	30	A/V	T	I
PGI$_2$	Veins	4·6 (0·1)	4·7 (0·1)	4·6 (0·2)	5·2 (0·1)	<0·0001	<0·01	NS
	Arteries	4.0 (0·2)	3·9 (0·2)	4·1 (0·2)	4·2 (0·2)		<0·01	
6-keto-PGI$_{1\alpha}$	Veins	3·9 (0·1)	4·3 (0·1)	4·4 (0·1)	4·8 (0·1)	<0·0001	<0·0001	NS
	Arteries	3·0 (0·2)	2·8 (0·3)	3·3 (0·2)	3·7 (0·3)		<0·0001	
TXB$_2$	Veins	0·3 (0·1)	0·6 (0·2)	0·8 (0·2)	1·2 (0·2)	NS	<0·0001	<0·02
	Arteries	0·6 (0·3)	0·4 (0·2)	0·6 (0·2)	0·7 (0·2)		NS	
$\frac{\text{6-keto-PGF}_{1\alpha}}{\text{TXB}_2}$	Veins	45·4 (8·3)	57·3 (12·3)	46·7 (10·7)	66·8 (20·2)	<0·005	NS	NS
	Arteries	17·8 (4·4)	18·9 (5·2)	18·5 (3·5)	25·2 (4·5)		NS	

Results are mean (SEM) values of 16 separate experiments

* A/V, Test for the main effect of the difference between arteries (A) and veins (V); T, orthogonal decomposition for linear trend of values with distance from the placenta; I, interaction between distance from placenta and the ratio of values in arteries:veins.

significantly different from the 12 other cords examined.

Discussion

The data included in Table 1 show that there is a reasonable agreement between the two assay methods used here: radioimmunoassay and bioassay. In this sense, and quantitatively too, our results are in agreement with those of Ritter *et al.* (1982), for umbilical arteries. Prostacyclin is known to be the major anti-aggregating agent produced by umbilical arteries (Ritter *et al.* 1982), and Mäkilä *et al.* (1983) have demonstrated a relation between umbilical PGI_2 production and blood flow in the human fetus. The present results, which supplement our previous findings (Benedetto *et al.* 1985*b*), demonstrate a gradient in the production of PGI_2 such that there is a higher production by umbilical veins and arteries close to the fetus compared with vessel rings taken close to the placenta. This gradient may reflect a progressive change in the properties of the endothelium towards a fetal character from placental-end to the fetal-terminus; umbilical arteries and veins have been shown to be associated with a higher rate of PGI_2 production compared with placental vessels (Kawano & Mori 1983).

Since the umbilical vessels are vital to fetal development and well-being, a high rate of production of PGI_2 appears advantageous to aid blood flow and to inhibit aggregation. In fact the values obtained for 6-keto-$PGF_{1\alpha}$ production by umbilical veins and arteries are much higher than have been found for adult vessels such as mammary veins (Benedetto *et al.* 1985*b*) and uterine veins (Kawano & Mori 1983).

Despite the gradient already noted in the production of 6-keto-$PGF_{1\alpha}$ in vessel rings, from placenta to fetus, the ratio of 6-keto-$PGF_{1\alpha}$:TXB_2 is approximately constant along the umbilical cord. The ratio (about 50 for umbilical veins and 20 for the corresponding arteries) is much greater than values for adult mammary vessels (ratio value about 5) (Benedetto *et al.* 1985*a*); Mäkila *et al.* (1983) and Mehta *et al.* (1982) also report similarly high values for the ratio in their studies on umbilical artery and vein, respectively. The high ratio in umbilical vessels possibly reflects a genuine antithrombotic mechanism that is important for fetal development. The higher value for the ratio in the umbilical vein compared with the artery is consistent with this concept. Additional support for this view comes from studies in pre-eclamptic pregnancies; in this condition there is a decreased production of PGI_2 by maternal and umbilical vessels (Bussolino *et al.* 1980; Massobrio *et al.* 1982) and, as found by Mäkilä *et al.* (1983), a lower umbilical blood flow is associated with a decreased ratio of production of 6-keto-$PGF_{1\alpha}$ in umbilical arteries. This proposed prostanoid mechanism for aiding umbilical blood flow would be additional to other well established features of fetal haemodynamics, such as the low concentrations of protein coagulation factors in the fetal circulation. These other features are known to be of major importance to the lower efficiency of the coagulation systems of fetal blood (Bleyer *et al.* 1971; Bonnar *et al.* 1971; Zilliacus *et al.* 1966).

Acknowledgments

We are grateful to the Italian 'Ministero della Pubblica Istruzione', and to the Association for International Cancer Research for financial support. We expressed our thanks to Dr J. Salmon of the Wellcome Research Laboratories (Beckenham, UK) for generously providing antisera and expert advice, and to Dr J. Pike (Upjohn Company, Kalamazoo, Michigan, USA) for a generous gift of prostacyclin.

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Received 30 December 1986
Accepted 25 February 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol 94, pp. 1170–1177

Maternal fat stores and fat accretion during pregnancy in relation to infant birthweight

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Summary. Maternal fat stores and fat accretion during pregnancy were estimated from body weight and skinfold thicknesses and by the factorial method in a sample of 56 Swedish women in their second pregnancies who gave birth to singletons at term. Prepregnancy lean body mass, and not fat mass, were strongly correlated with infant birthweight. Total weight gain was significantly correlated with infant birthweight. A wide range of maternal fat accretion during pregnancy was observed, and the amount of fat accumulated was related to the total weight gain. In spite of this, maternal fat accretion during pregnancy was found to have little bearing on the infant birthweight at term.

There is a significant correlation between maternal anthropometric values before and during pregnancy and the birthweight of the offspring. Thus prepregnancy weight is positively correlated with infant birthweight even after maternal height has been taken into account (Dougherty & Jones 1982; Langhoff-Roos *et al.* 1987). Maternal height, however, when considered independently of prepregnancy weight, seems to lose its significant correlation with infant birthweight in some populations (Langhoff-Roos *et al.* 1987; Rantakillio & Hartikainen-Sorri 1981), but not in others (Dougherty & Jones 1982; Thomson *et al.* 1968).

Weight gain during pregnancy is also positively correlated with infant birthweight independently of prepregnancy weight (Rantakallio & Hartikainen-Sorri 1981), when the mother is not excessively overweight (Abrams & Laros 1986).

Since both prepregnancy weight and weight gain during pregnancy are usually independently correlated with infant birthweight (Naeye 1981; Ounsted & Scott 1981), the question arises as to which component of prepregnancy weight and weight gain has the closest association with intra-uterine growth.

This study was designed to investigate the relation between maternal fat depots at the onset of pregnancy, fat accretion during pregnancy and infant birthweight at term.

Subjects and methods

Selection of subjects

Since infant birthweight is the outcome variable in this study, it was considered desirable to select women who would be expected to give birth to infants whose birthweights would cover a wide range. Infant birthweight may be predicted early in pregnancy by a variety of factors, of which prepregnancy weight and birthweight of older siblings are important (Bakketeig *et al.* 1979; Dougherty & Jones 1982). To test the predictive value of these two factors, we reviewed a retrospective series of 187 consecutive women who gave birth to their second child in the period 1 January to 1 March, 1984 at the Department of

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Obstetrics and Gynaecology, University Hospital, Uppsala. It was found that the birthweight of the first infant was a stronger predictor of that of the second infant than the prepregnancy weight of the mother.

On the basis of this finding three equal groups of women in their second pregnancy, whose first baby born at term weighed (i) <3100 g, (ii) between 3400 and 3600 g and (iii) >4000 g were selected during the period 1 January to 1 August, 1985. The participants were healthy Swedish women attending for antenatal care before 15 weeks gestation at units covering the main parts of Uppsala and surroundings. Overall, 147 women were eligible in terms of the birthweight of their first babies, and after explanation of the study 77 showed interest in joining it. Four of them had a miscarriage before 17 weeks gestation. The remaining 73 women were contacted and invited to join the study; 71 accepted, and of these, nine changed their minds before entering and two dropped out during the study.

A total of 60 pregnant primiparae underwent investigations, four of whom were later excluded because of complications during pregnancy (premature delivery in three and hypertension in one). Thus 56 healthy Swedish pregnant primiparae formed the basis of the analyses.

The 70 eligible women who did not wish to participate did not differ significantly from the study group in social status or maternal prepregnancy weight and height. In relation to the birthweight of the first infant total weight gain in pregnancy and infant birthweight was not different from that of the study group.

Study design

Information was obtained regarding the social and medical history, prepregnancy weight, and smoking habits during pregnancy. Clinical examinations during the study, including ultrasound measurements, were performed by one of the authors (J.L.-R.) and the same midwife. Visits to the hospital for measurements and clinical examination took place at 16, 17, 25, 32, 33 and 37 weeks gestation, at delivery, and 3 days and 8 weeks postpartum. Length of gestation was determined by ultrasonic measurement of fetal biparietal diameter at week 17.

Clinical examination

Clinical examination included maternal weight determination with a standardized weighing scale (to the nearest 0·1 kg) at weeks 17, 25, 33 and 37, at delivery and 3 days and 8 weeks postpartum. At weeks 17 and 37 skinfolds (biceps, triceps, subscapular and supra-iliac) were measured with a measuring tape and a Harpenden caliper. (In two cases skinfold measurements were not recorded at week 37.)

The prepregnancy weight was reported by the woman at her first visit to the antenatal care unit. The given prepregnancy weight cannot be exactly validated, but its relation to measured body weights in early pregnancy can give some indication of its value. The difference between prepregnancy weight and the body weight measured at the first antenatal visit, at an average of week 10·5, was 2·2 (SD 1·8) kg. Although the coefficient of variation seems high, it was even higher when the difference between the body weight at weeks 17 and 10·5 was calculated. Furthermore, the difference between reported prepregnancy weight and body weight measured at week 10·5 was not significantly correlated with prepregnancy weight. The above considerations suggest that the reported prepregnancy weight in our study group was a reasonable estimate of the true prepregnancy weight.

Weight gain during pregnancy for a given length of gestation was calculated as the difference between the body weight at that point and the prepregnancy weight as reported by the woman.

Total weight gain was calculated as the difference between the weight on admission to the delivery ward and the prepregnancy weight

Retained weight gain (increase in weight during pregnancy mainly due to deposition of extra tissue and tissue fluid in the mother) was defined as the difference between the weight 3 days postpartum and the prepregnancy weight. (Information on body weight 3 days postpartum was missing in two cases.) The body weight 3 days postpartum was chosen for practical reasons, as the length of the postpartum stay at the hospital is 3–6 days. Retained weight gain at this point reflects maternal fat accretion during pregnancy, residual pregnancy-induced tissue changes and a variable degree of involution of the uterus and engorgement of the breasts. Large individual variations were observed in the contribution of these components in the first

Table 1. Characteristics of the 56 women in the study group

	Mean	SD	Range
Age (years)	28·8	4·8	21–40
Prepregnancy weight (kg)	61·8	10·1	39·0–95·0
Height (cm)	166·9	5·9	155–180
Sum of skinfolds* (mm)	64·8	22·5	27·0–114·0
Lean body mass† (kg)	42·8	5·4	27·1–58·0
Fat mass† (kg)	19·0	5·8	9·2–37·0
First pregnancy:			
Infant birthweight (g)	3637	694	2280–5140
Second pregnancy:			
Infant birthweight (g)	3718	591	2620–6020
Gestational age‡ (days)	280·3	8·9	259–294
Total maternal weight gain (kg)	14·8	4·7	1·2–25·0

* Sum of biceps, triceps, subscapular and supra-iliac skinfolds at week 17.

† Approximated by use of prepregnancy weight and the sum of four skinfold thicknesses at week 17

‡ Length of gestation at delivery according to ultrasound measurement in week 17.

days postpartum, evident from the difference between retained weight gain 3 days postpartum and total weight gain minus infant birthweight and weight of placenta. The mean difference was 1·3 (SD 1·5, range −3·4 to 4·1) kg.

Maternal fat stores and fat accretion

Lean body mass and fat mass in early pregnancy were calculated from the prepregnancy weight and skinfold thicknesses (biceps, triceps, subscapular and supra-iliac) at week 17, using the equations proposed by Durnin & Womersley (1974) for non-pregnant women.

Maternal fat accretion was estimated on the bases of:

(i) Retained weight gain 3 days postpartum

(ii) The amount of total weight gain exceeding the weight of the infant and placenta and an estimate of other pregnancy-induced tissue changes, using the equation proposed by Hytten & Leitch (1971), modified by multiplying the estimated amount (except the increase of the breasts, 405 g) by the infant birthweight divided by 3400. This way of partitioning has been called the factorial method.

(iii) Differences in fat mass between week 37 and early pregnancy, calculated from body weights and skinfold thicknesses. The fat mass in early pregnancy was calculated on the basis of prepregnancy weight and four skinfold thicknesses (biceps, triceps, subscapular and supra-iliac) at week 17 by means of equations proposed by Durnin & Womersley (1974). Fat mass in week 37 was calculated in the same way from the body weight and skinfold thicknesses at week 37.

The coefficients of correlation between the three different estimates of fat accretion were between 0·76 and 0·94.

Results

Characteristics of the study population are listed in Table 1.

Fifteen women were smokers at week 17. Smokers were compared with non-smokers with respect to infant birthweight, total weight gain, retained weight gain 3 days postpartum, prepregnancy weight and its components of fat mass and lean body mass, maternal height and fat accretion estimated by both the factorial and skinfold methods. Since the differences between smokers and non-smokers were not statistically significant, the groups were combined for further analysis.

The coefficient of correlation (r) between the birthweight of the first infant and the second infant in the study group was 0·67. The standard deviation of the infant birthweight decreased from 694 g to 591 g, which is still considerably higher than that of an unselected sample.

Table 2 shows a matrix of correlations with corresponding P values. The variables included are birthweight of second infant, prepregnancy weight and height, lean body mass at beginning of pregnancy, total weight gain in pregnancy and retained weight gain 3 days postpartum. Women giving birth to large babies tended to be taller and to have a higher prepregnancy weight than those with smaller babies. This difference in body size between the mothers was not accounted for by their initial fat mass alone. There was a significant positive relation between infant birthweight and total weight gain, but not between infant birthweight and retained weight gain.

In a model of multiple linear regression with infant birthweight as the dependent variable and lean body mass and fat mass in early pregnancy and total weight gain as independent variables, fat mass did not correlate significantly with infant birthweight (P 0·346 and regression

Table 2. Matrix of correlations between birthweight of second infant (IBW), maternal prepregnancy weight (PPW) and height (MH), lean body mass (LBM) and fat mass (FM) in early pregnancy, total weight gain (TWG) and retained weight gain 3 days postpartum (RWG)

		IBW	PPW	MH	LBM	FM	TWG	RWG
IBW		—						
PPW	*r*	0·30						
	P	*0·02*	—					
	n	56						
MH	*r*	0·33	0·55					
	P	*0·01*	*0·01*	—				
	n	56	56					
LBM	*r*	0·35	0·90	0·69				
	P	*0·01*	*0·01*	*0·01*	—			
	n	56	56	56				
FM	*r*	0·20	0·91	0·33	0·64			
	P	*0·14*	*0·01*	*0·01*	*0·01*	—		
	n	56	56	56	56			
TWG	*r*	0·39	0·05	0·16	−0·04	0·13		
	P	*0·01*	*0·69*	*0·24*	*0·79*	*0·35*	—	
	n	56	56	56	56	56		
RWG	*r*	0·14	0·02	0·14	−0·10	0·14	0·92	
	P	*0·33*	*0·88*	*0·31*	*0·45*	*0·32*	*0·01*	—
	n	54	54	54	54	54	54	

The values shown are the correlation coefficient (*r*), *P* value (in italics) and number of pairs of variables analysed (*n*).

coefficient −15·0 g/kg), as did lean body mass and total weight gain (Table 3). Also, infant birthweight was determined (R^2) to practically the same extent when maternal fat mass was omitted as an independent variable.

Table 3. Multiple linear regression analysis of infant birthweight with lean body mass, fat mass and total weight gain as independent variables. Values for fat mass and lean body mass were obtained from the prepregnancy weight and the skinfold thicknesses at week 17

	Regression coefficient (SE)	*P* value
Lean body mass	50·4 (16·8)	0·004
Fat mass	−15·0 (15·3)	0·346
Total weight gain	53·3 (14·3)	0·001

Coefficient of determination (R^2) = 29·8%

	Regression coefficient (SE)	*P* value
Lean body mass	39·9 (12·7)	0·003
Total weight gain	50·5 (14·5)	0·001

Coefficient of determination (R^2) = 28·6%

For the purpose of further characterization, the women were divided into three groups according to pregnancy outcome, namely infant birthweight and retained weight gain.

Figure 1 shows the changes in body weight for mothers of infants with birthweights of: (i) <3200 g, (ii) between 3200 and 4100 g and (iii) >4100 g. At week 17 the weight gain in the group of women giving birth to infants above 4100 g was significantly lower than that in the others ($P<0·01$). Furthermore, women who gave birth to large infants displayed an accelerated weight gain during the rest of pregnancy and a greater loss in the postpartum period. The difference 8 weeks postpartum, however, was not statistically significant.

Figure 2 shows the changes in body weight for groups of women with a retained weight gain 3 days postpartum of: (i) <6·0 kg, (ii) between 6·0 and 12·0 kg and (iii) >12·0 kg. Throughout pregnancy and after delivery there were consistently large differences in weight gain between the groups, but the infant birthweights were similar.

Table 4 shows the fat accretion estimated by the three methods used. It seemed that the estimates obtained by skinfold and factorial methods were similar, while the retained weight

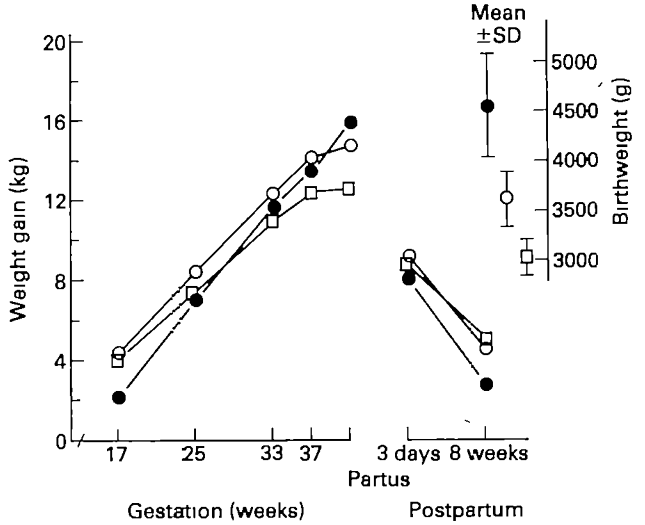

Fig. 1. Maternal weight gain during pregnancy and the puerperium in groups of women who gave birth to infants of different birthweights Birthweight ≤3200 g (n = 11) (□); 3200–4100 g (n = 33) (○); ≥4100 g (n = 12) (●).

gain 3 days postpartum was about twice as high as the other values.

Figure 3 illustrates fat accretion estimated by these different methods in relation to the total maternal weight gain in the three infant-birthweight groups. Although the infant birthweight differed considerably between the groups, the fat accretion was almost the same irrespective of the method used.

The fat accretion in groups of women who

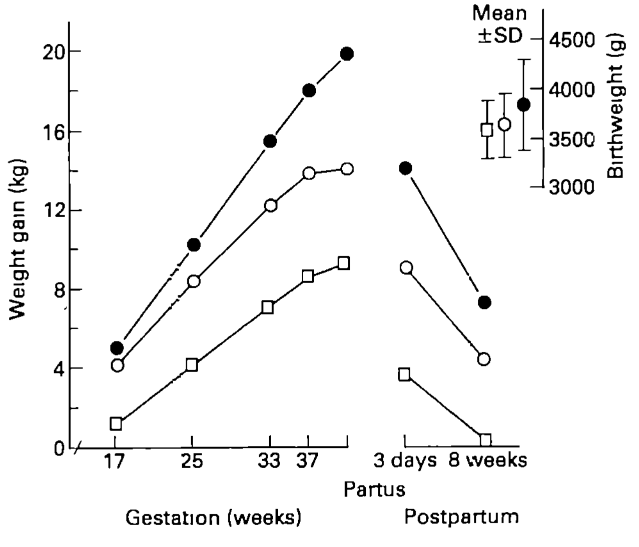

Fig. 2. Maternal weight gain during pregnancy and the puerperium and infant birthweight in groups of women who retained different amounts of weight gained 3 days postpartum Retained weight gain ≤6·0 kg (n = 14) (□); 6·0–12·0 kg (n = 25) (○); ≥12·0 kg (n = 15) (●).

Table 4. Fat accretion estimated on the basis of the retained weight gain 3 days postpartum, by the factorial method*, and by the difference in fat mass calculated by use of three or four skinfold thicknesses at weeks 17 and 37, the prepregnancy weight and the body weight at weeks 17 and 37

	Mean	SD	Range
Retained weight gain 3 days postpartum (kg)	9·0	4·4	−4·0–18·4
Factorial estimate (kg)	4·9	4·4	−10·0–13·6
Skinfold estimate (kg)†	5·0	2·7	−3·0–10·0
Skinfold estimate (kg)‡	5·2	2·5	−1·1–10·4
Skinfold estimate (kg)§	3·8	2·6	−3·2– 9·9
Skinfold estimate (kg)¶	4·0	2·3	−1·2– 9·3

* Hytten & Leitch (1971)

† Difference between fat mass calculated by use of three skinfolds (biceps, triceps and subscapular) at weeks 17 and 37 and prepregnancy weight and body weight at week 37.

‡ Same as † but four skinfolds used (biceps, triceps, subscapular and supra-iliac).

§ Difference between fat mass calculated by use of three skinfolds (biceps, triceps and subscapular) at weeks 17 and 37 and body weight at weeks 17 and 37.

¶ Same as § but four skinfolds used (biceps, triceps, subscapular and supra-iliac).

retained different amounts of weight gained is illustrated in Fig. 4. The changes in fat accretion on the basis of retained weight gain were paralleled by those estimated by both of the other methods.

Discussion

The object of the present study was to relate fetal growth to maternal prepregnancy fat stores and fat accretion during pregnancy. Admittedly these relations are highly complicated and intertwined and involve a large number of processes at maternal, placental and fetal levels.

The positive linear relation between prepregnancy weight and infant birthweight in our sample is in accordance with that found in many other studies (Abrams & Laros 1986; Dougherty & Jones 1982; Eastman & Jackson 1968; Peckham & Christianson 1971; Simpson *et al.* 1975).

The prepregnancy weight in a woman is significantly positively correlated with her own birthweight (Klebanoff *et al.* 1984; Langhoff-Roos *et al.* 1987; Magnus *et al.* 1984), but the effect of the prepregnancy weight on infant birthweight persists even when her own birthweight is taken into account as part of a multiple regression analysis (Langhoff-Roos *et al.* 1987). Thus, part of the correlation between prepregnancy weight and infant birthweight might be due to 'heredity of birthweight'.

Another way to explain the relation between infant birthweight and maternal prepregnancy weight might be that the maternal fat stores or disposition towards fat accretion before pregnancy affect fetal growth. This disposition could be influenced by hormonal or nutritional factors acting on both prepregnancy fat deposition and fetal growth.

When prepregnancy weight was divided into lean body mass and fat mass, it was only lean body mass that correlated significantly with infant birthweight. This rather supports the idea that lean body mass is hereditarily determined, and that in this population heredity has a main influence on fetal growth.

The positive correlation between weight gain in pregnancy and infant birthweight is known, at least when the prepregnancy weight is normal or below normal (Abrams & Laros 1986; Eastman & Jackson 1968; Ounsted & Scott 1981; Simpson *et al.* 1975), although in the study by Ancri *et al.* (1977) this relation was not confirmed. It has to be borne in mind that in most investigations of the relation between infant birthweight and pregnancy weight gain, infant birthweight has been included as part of the total weight gain in the analysis (Abrams & Laros 1986; Eastman & Jackson 1968; Simpson *et al.* 1975). A simple correction obtained by subtraction of infant birthweight and placenta in order to establish a 'net gain' has been used (Naeye 1981; Ounsted & Scott 1981).

Earlier reports on pregnancy weight gain and infant birthweight give no information about the relation between maternal fat accretion and infant birthweight, as weight gain has not been broken down into its different components. In the present study fat storage in pregnancy was estimated by simple anthropometric measurements, although none of the three methods that we used to estimate fat accretion is without inherent problems.

Retained weight gain 3 days postpartum includes increased weight due to the enlarged uterus and breasts, increased blood volume and residual oedema.

In the present study, the calculation of fat mass from skinfold measures used equations

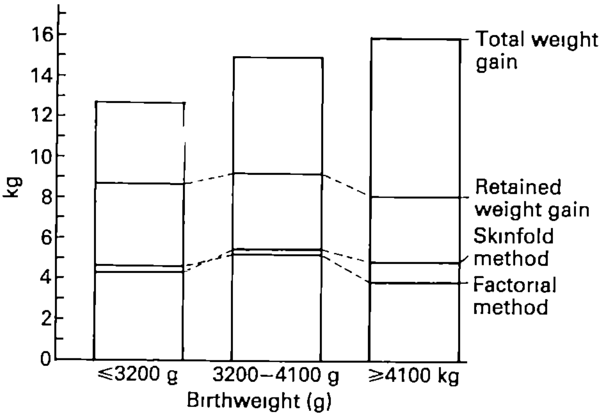

Fig. 3. The relation between total weight gain, retained weight gain 3 days postpartum and maternal fat accretion, estimated by the factorial method and from skinfold measurements in groups of women who gave birth to infants of different birthweights.

constructed by analysis of a sample of non-pregnant women (Durnin & Womersley 1974). No studies to validate these in pregnant women have been reported. Three of the skinfolds which we measured and used for calculation (biceps, triceps and subscapular) are among those which change least during early pregnancy (Taggart *et al.* 1967). Thus the extrapolation of skinfold thicknesses from week 17 to the pre-pregnant state can be justified, but the change in fat depots during pregnancy might be underestimated by this procedure. Oedema in the subcutaneous tissue, however, might result in an increase in skinfold thicknesses, leading to overestimation of the amount of fat tissue

The estimates made by the factorial method are standardized and do not reflect inter-individual variation not accounted for by the variation in infant birthweight.

Even though we are aware of the shortcomings of these methods, all three give us a similar picture of a large inter-individual variation of fat accretion during pregnancy which is not related to infant birthweight.

Maternal fat accumulates predominantly in the first part of pregnancy and fetal growth is greatest in the last part (Hytten & Leitch 1971). Women who gave birth to large infants showed a lower weight gain at week 17, even though their total weight gain was larger than the mean for the whole group. This may be regarded as yet another indication that maternal fat accretion

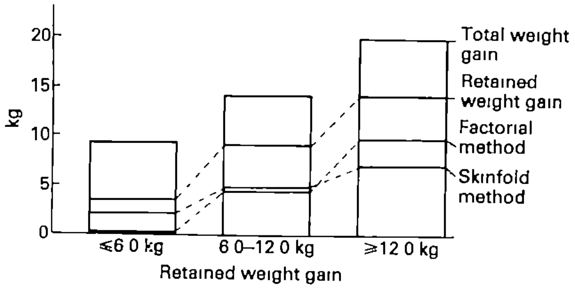

Fig. 4. The relation between total weight gain, retained weight gain 3 days postpartum and maternal fat accretion, estimated by the factorial method and from skinfold measurements in groups of women who retained different amounts of gained weight 3 days postpartum.

during pregnancy and fetal growth are separate processes which are unrelated in a sample of well-nourished Swedish women.

It could be argued that even when we confine ourselves to term pregnancies, some variables in this study are related to length of gestation. Assuming a linear relation, this influence could easily be taken into account as length of gestation was determined by ultrasound measurements in all cases. However, even after adjusting infant birthweight and total weight gain for length of gestation, the results of the present study were similar and the conclusions remained the same.

Why then, did we not find a correlation between such a wide range of maternal fat accretion and fetal growth? Fat accretion during pregnancy is basically required to provide a guarantee of energy supply for the fetus in situations in which the mother is in negative energy balance. Our results suggest that no benefit to the fetus is obtained from the maternal fat depot as long as the basic needs for fetal growth can be met by the daily food intake.

Acknowledgments

This study was partly supported by a grant from the First of May Flower Annual Campaign for Children's Health. Midwife Synnöve K. Jansson is thanked for her assistance during the study.

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Received 13 February 1987
Accepted 9 June 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1178–1185

Energy intake and physical activity during pregnancy in relation to maternal fat accretion and infant birthweight

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Summary. During the second pregnancy of 56 Swedish women resulting in a term birth, energy intake and physical activity were measured for 3 days at weeks 17 and 33. The values were related to maternal lean body mass, pregnancy weight gain, maternal fat accretion and infant birthweight by multiple linear regression analyses. A significant regression coefficient was found for energy intake at week 17 on maternal fat accretion. Energy intake was not significantly correlated with infant birthweight, not even when physical activity and maternal lean body mass were taken into account. Thus in a well-nourished Swedish population, energy intake is positively related to maternal fat accretion but not to the birthweight of term infants.

The relations between energy intake during pregnancy and maternal fat accretion and infant birthweight have been discussed for many years. Advice given to the pregnant woman has varied from 'eating for two' to restrained intake in order to minimize weight gain during pregnancy, either to have a smaller baby for easy delivery or to avoid obesity or even pre-eclampsia. However, the scientific basis of these recommendations is very weak (Enkin & Chalmers 1982).

In general, accumulation of body fat is affected by energy balance, but the unique extra fat store associated with pregnancy may or may not be related to a change in energy balance in the same way. In available reports, energy intake and physical activity have not been considered simultaneously, which makes it difficult to determine their interaction. Total pregnancy weight gain includes not only fat accretion, but the weight of the product of conception and a considerable amount of maternal tissue and fluid gained during pregnancy, which is lost at delivery or in the early postpartum period. Thus while many of the components of weight gain will be related to it, they will not necessarily be related to each other.

This study was designed to elucidate the relation between dietary intake, physical activity and maternal fat accretion during pregnancy on the one hand, and infant birthweight on the other, in an affluent Western society.

Subjects and methods

This study forms part of a comprehensive investigation of energy metabolism during pregnancy in Swedish women. Details of the overall study design are given by Langhoff-Roos *et al.* (1987*a*). In brief, 56 healthy Swedish women undergoing a normal second pregnancy leading to a term birth formed the study group.

Clinical examination included weighing with a standardized weighing scale to the nearest 0·1 kg

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at weeks 17, 25, 33 and 37, at delivery, and 3 days and 8 weeks postpartum. At weeks 17 and 37 skinfold thicknesses (biceps, triceps, subscapular and supra-iliac) were measured with a Harpenden caliper. The prepregnancy weight was reported by the woman at her first visit to the antenatal clinic. Total weight gain was calculated as the difference between the weight on admission to the delivery ward and the prepregnancy weight.

During the first part of the pregnancy (including week 17), 48 of the 56 women were gainfully employed, and at week 33, 22 were still working. The type of work ('social class') was similar in the group of women who entered the study and those who did not want to participate. Physical exercise of a moderate degree (gymnastics, football and swimming, but not competitive sports) was performed by ten women about once a week during early pregnancy.

Dietary intake

Recording of dietary intake is considered more reliable than recall (Block 1982). Three days of recording was considered to be the optimal time span in our investigation, since further extension of the food recording could have compromised the accuracy of the recordings. This decrease in accuracy might exceed the gain provided by more extended recording, which could diminish the importance of the day-to-day variability. On the other hand, self-induced restriction or selection of food intake at the time of recording would be reduced by recording for more than 3 days.

Food intake was recorded for 3 consecutive days from Monday to Wednesday or from Tuesday to Thursday in weeks 17 and 33. Everything the woman ate or drank during this period was measured with household measures or estimated by means of a guide, and the intake recorded. The pregnant women were instructed by an experienced nutritionist at weeks 16 and 32 how to measure or estimate their food intake. To facilitate estimates of intake and obtain conformity in the records, a guide was given to the women. In addition to precise descriptions of the food and liquid intake, the food records showed the time of the intake.

It was intended that recordings of food intake and physical activity should take place on days representative of the period chosen. The women were later asked if the days of recording of their dietary intake and physical activity were representative of the period. In a few cases this was not so and a new recording was made in the following week. (Information on dietary intake was missing in two cases at weeks 17 and 33.)

The recorded food consumption was converted to measures of energy and nutrient intake on the basis of Food Composition Tables compiled by the Swedish National Food Administration (1978).

Physical activity

The usual way of estimating daily physical activity is to record the type and duration of the activity in a diary which are later converted into oxygen consumption from tables. We chose to measure physical activity with an actometer instead of the diary method because we thought it would be troublesome for the women to record both the food intake and physical activity accurately at the same time.

Physical activity was measured during the food-recording periods with two actometers, one attached to the wrist of the dominant arm, and the other to the ankle of the same side. Actometers are calendar wrist-watches which convert the magnitude of acceleration to 'time' (Schulman & Reisman 1959; Saris & Binkhorst 1977). Accelerometers are superior to movement counters when used to estimate oxygen consumption during walking, running or standardized exercises (Montoye *et al.* 1983). They have also been validated by comparison with described activity (Saris & Binkhorst 1977; J. Langhoff-Roos *et al.*, unpublished observations) and with oxygen consumption calculated on the basis of activity descriptions (Saris & Binkhorst 1977).

The time on the actometers was read three times a day over a period of 72 h. The estimate of physical activity during the period was operationally defined as the sum of the 'time' measured by both actometers (unit = 24 h). (Information on physical activity was missing in four cases at week 17 and in two cases at week 33.)

Energy intake

Energy intake is presented as crude or adjusted intake. Crude energy intake is the mean daily intake of energy for the recording period. The energy intake has been adjusted in two ways.

First, adjustment for the physical activity measured at the same time as the recording of energy intake. As energy expenditure by physical activity is considered to be about one third of the energy used to sustain basal metabolism in an affluent society (Prentice *et al.* 1985), we have divided energy intake by (3+ the ratio between the individual's physical activity and the mean activity of the whole study group). Second, adjustment for both physical activity and lean body mass was made by also dividing by lean body mass at week 17 and week 37. The reason for this is the positive correlation between lean body mass and basal metabolic rate (Blaxter 1985).

Fat accretion

Fat accretion during pregnancy was estimated as the difference between fat mass in early pregnancy and at week 37. Fat mass in early pregnancy was calculated on the basis of the prepregnancy weight and four skinfold measurements (biceps, triceps, subscapular and suprailiac) in week 17 using the equations of Durnin & Womersley (1974). Fat mass at week 37 was calculated in the same way from the body weight and skinfold measurements at that week.

Results

Fifteen women were smokers at week 17. Smokers were compared with non-smokers with respect to prepregnancy weight, fat mass and lean body mass, height, total weight gain, infant birthweight, fat accretion by skinfold methods, energy intake (crude and adjusted) and physical activity at weeks 17 and 33. There were no statistically significant differences between the groups and they were combined for further analysis

The distributions of energy intake (crude and adjusted) and physical activity at weeks 17 and 33 are shown in Table 1. Energy intake, both crude and adjusted for physical activity, increased from week 17 to week 33 by about 3%. When adjusted for both physical activity and lean body mass, energy intake decreased by about 11% during the same period of time. The coefficient of variation of energy intake was about 20% even after adjustments Physical activity decreased by about 6% from week 17 to 33. Energy intake adjusted for both physical activity and lean body mass was the only variable that differed with a statistically significant fall between weeks 17 and 33.

In Table 2 the relation between energy intake, physical activity and lean body mass in early and late pregnancy is presented in the form of a matrix of correlations. As expected, the values of energy intake and physical activity at week 17 were positively correlated with those obtained at week 33 ($P<0{\cdot}01$). The correlation between energy intake and physical activity measured at the same time was also positive, but not statistically significant (week 17: $P=0{\cdot}13$; week 33: $P=0{\cdot}12$). A weak significantly positive correlation was found between physical activity at week 17 and energy intake at week 33 ($P=0{\cdot}02$).

The correlations between infant birthweight and maternal fat accretion, on the one hand, and energy intake (crude and adjusted) and physical activity, on the other, are shown in Table 3. A significantly positive but weak linear relation was found at week 17 between maternal fat accretion and energy intake adjusted for physical activity.

In Table 4 total weight gain is analysed by multiple linear regression. Mean energy intake and physical activity, and lean body mass in early pregnancy were used as independent variables. No statistically significant relation was found between any of these variables and total weight gain.

The results of multiple linear regression analyses of infant birthweight are given in Table 5. The independent variables were energy intake, fat-free mass and physical activity at weeks 17 and 33. Only lean body mass (in both early and late pregnancy) was significantly related to infant birthweight.

Table 6 gives the results of corresponding analyses with maternal fat accretion as the dependent variable. The only significant association found was a positive correlation between energy intake at week 17 and fat accretion.

Discussion

Dietary intake is difficult to measure and the very fact of measuring it may affect the amount and the quality of the food taken. We chose the method of 3-days food recording to reduce inconvenience to the woman. We decided upon weeks 17 and 33 for the dietary records in order to describe two periods of predominant maternal storage and fetal growth respectively (Hytten & Leitch 1971)

Table 1. Energy intake and physical activity at weeks 17 and 33

	n	Mean	SD	Range
Week 17				
Crude (MJ/day)	54	9·21	1·67	6·02–13·66
Adjusted† (MJ/unit/day)	51	2·31	0·42	1·53– 3·35
Adjusted‡ (MJ/unit/day/kg × 10³)	51	52·0 *	10·6	27·2 –77·1
Physical activity (units/day)	52	42·6	11·1	20·7 –61·0
Week 33				
Crude (MJ/day)	54	9·48	1·70	5·90–13·87
Adjusted† (MJ/unit/day)	54	2·38	0·42	1·60– 3·38
Adjusted‡ (MJ/unit/day/kg × 10³)	52	46·4 *	9·7	30·5 –68·9
Physical activity (units/day)	54	39·8	11·8	19·7 –73·0

* This difference was statistically significant (*P* <0·01).
† Adjusted for physical activity.
‡ Adjusted for both physical activity and lean body mass.

Table 2. Matrix of correlations between physical activity (PA) and energy intake (EI) at weeks 17 and 33, and lean body mass (LBM) at weeks 17 and 37

		EI 17	EI 33	PA 17	PA 33	LBM 17	LBM 37
EI		—					
Week 33	*r*	0·48					
	P	*0·01*	—				
	n	53					
PA							
Week 17	*r*	0·22	0·32				
	P	*0·13*	*0·02*	—			
	n	51	51				
Week 33	*r*	0·03	0·21	0·57			
	P	*0·81*	*0·12*	*0·01*	—		
	n	53	54	51			
LBM							
Week 17	*r*	−0·02	0·12	−0·02	0·04		
	P	*0·90*	*0·39*	*0·90*	*0·77*	—	
	n	54	54	52	54		
Week 33	*r*	−0·15	0·02	0·01	0·05	0·93	
	P	*0·30*	*0·89*	*0·96*	*0·75*	*0·01*	—
	n	52	52	50	52	54	

The values shown are the correlation coefficient (*r*), the *P* value (in italics) and the number of observations (*n*)

It might be argued that it would be more interesting to relate energy intake to fetal growth instead of infant birthweight, on the one hand, and tissue deposition per week rather than total weight gain during pregnancy, on the other. To some degree this argument has been taken into account in the decision to study only term pregnancies. Furthermore, the analyses presented in this paper have been recalculated after adjusting infant birthweight and total weight gain for length of gestation, assuming linear relations. The results were similar to those presented above and the conclusions the same. Thus, what is found concerning infant birthweight in this study can also be applied to fetal growth.

Several authors have investigated the relation between energy intake and weight gain during pregnancy. Some have found a statistically significant correlation (Beal 1971; Thomson 1959; Picone *et al.* 1982*b*) and others have not (Ancri *et*

Table 3. Coefficients of correlation between infant birthweight and maternal fat accretion, on the one hand, and energy intake and physical activity at weeks 17 and 33, on the other

		Infant birthweight		Maternal fat accretion	
		Week 17	Week 33	Week 17	Week 33
Crude	r	−0·06	−0·05	0·26	0·24
	P	*0·65*	*0·71*	*0·07*	*0·09*
	n	54	54	52	52
Adjusted (1)	r	−0·08	−0·05	0·31	0·19
	P	*0·58*	*0·73*	*0·03*	*0·17*
	n	51	54	49	52
Adjusted (2)	r	−0·22	−0·23	0·19	0·13
	P	*0·12*	*0·10*	*0·18*	*0·36*
	n	51	52	49	52
Physical activity	r	0·01	−0.01	0·01	0·08
	P	*0·92*	*0·93*	*0·95*	*0·57*
	n	52	54	50	52

Energy intake is presented as crude and adjusted for physical activity (1) or for both physical activity and lean body mass (2).

The values shown are the correlation coefficient (r), P values (in italics) and the number of pairs analysed (n).

Table 4. Multiple linear regression analysis of total weight gain, with energy intake, physical activity and lean body mass as independent variables

Model: Total weight gain (kg) = $k + a \times$ energy intake (MJ) +
$b \times$ lean body mass (kg) +
$c \times$ physical activity (units/day)

(n = 50)	Regression coefficient (SE)	P value
Energy intake	−0·303 (0·497)	0·545
Lean body mass	0·009 (0·146)	0·953
Physical activity	0·008 (0·025)	0·757
Coefficient of determination = 0·9%		

Values of energy intake and physical activity are mean values of observations in weeks 17 and 33 Lean body mass is calculated from prepregnancy weight and skinfold thicknesses in week 17

al. 1977; Papoz *et al.* 1981). Papoz *et al.* (1981) observed a statistically significant positive relation between the increase in dietary intake during the first 6 months of pregnancy (compared with the prepregnancy intake) and the total weight gain. We know of no published studies in which fat accretion during pregnancy has been related to energy intake.

In well-nourished populations some investigations have shown an increase in infant birthweight with energy intake (Thomson 1959; Picone *et al* 1982*a*). In the study by Thomson (1959), the relation between infant birthweight and energy intake practically disappeared (r = 0·05) when maternal body weight at week 20 was taken into account. In other studies no significant relation was found between infant birthweight and energy intake (Beal 1971; Ancri *et al.* 1977).

Physical activity might affect maternal fat accretion and fetal growth by two different mechanisms—energy restriction or redistribution of blood flow. It has been suggested that in developing countries excess physical activity may reduce the maternal weight gain and infant birthweight (Tafari *et al.* 1980). Some studies in industrialized countries have reported that working in the last trimester was associated with a reduction in infant birthweight by 150–400 g (Naeye & Peters 1982; Alegre *et al.* 1984). Other

Table 5. Multiple linear regression analyses of infant birthweight, with energy intake, lean body mass and physical activity at weeks 17 and 33 as independent variables

Model: Infant birthweight (g) = $k + a \times$ energy intake (MJ) +
$b \times$ lean body mass (kg) +
$c \times$ physical activity (units/day)

Week 17 ($n = 51$)	Regression coefficient (SE)	P value
Energy intake	−21·8 (50·3)	0·667
Lean body mass	42·4 (19·3)	0·033
Physical activity	1·27 (7·68)	0·870

Coefficient of determination = 11·4%

Week 33 ($n = 52$)	Regression coefficient (SE)	P value
Energy intake	−12·7 (45·8)	0·783
Lean body mass*	44·5 (13·3)	0·002
Physical activity	−1·22 (6·53)	0·853

Coefficient of determination = 17·0%

* As skinfold measurements in late pregnancy were available only for week 37, the analysis for lean body mass concerns that week

Table 6. Multiple linear regression analyses of maternal fat accretion during pregnancy with energy intake, lean body mass and physical activity as independent variables Maternal fat accretion was estimated by the difference in fat mass between early and late pregnancy

Model: Fat accretion (kg) = $k + a \times$ energy intake (MJ) +
$b \times$ lean body mass (kg) +
$c \times$ physical activity (units/day)

Week 17 ($n = 49$)	Regression coefficient (SE)	P value
Energy intake	0·466 (0·211)	0·033
Lean body mass	0·110 (0·080)	0·175
Physical activity	−0·028 (0·033)	0·407

Coefficient of determination = 12·4%

Week 33 ($n = 52$)	Regression coefficient (SE)	P value
Energy intake	0·334 (0·209)	0·116
Lean body mass*	0·023 (0·060)	0·702
Physical activity	0·006 (0·030)	0·848

Coefficient of determination = 6·0%

* As skinfold measurements in late pregnancy were available only for week 37, the analysis for lean body mass concerns that week.

studies (Murphy *et al.* 1984; Saurel & Kaminski 1983; Marbury *et al.* 1984) did not find a relation between low birthweight and employment during pregnancy. Briend (1980) found that a reduction in physical activity by bed rest, at least in the last trimester of pregnancy was associated with an increase in infant birthweight of about 200 g.

In the present study we have only considered dietary intake and physical activity as part of the energy balance during short periods of time. Our aim was to describe the relation between energy intake and physical activity, on the one hand, and maternal fat accretion and infant birthweight on the other, in two different ways. The first approach was that of linear correlations between the variables. The second approach was that of multiple linear regression analyses of maternal fat accretion and infant birthweight, with energy intake, physical activity and lean body mass as independent variables.

Maternal fat accretion was significantly and positively correlated with energy intake both as a simple correlation and by multiple linear regression analysis which showed that energy intake in week 17 was more strongly correlated with fat accretion than energy intake in week 33 (Table 6). This finding is in accordance with the assumption that fat accretion during pregnancy takes place mainly in the early part of pregnancy (Hytten & Leitch 1971).

The lack of a linear relation between energy intake (either crude or adjusted), physical activity and infant birthweight might be explained in several ways. First, the methods used in this study to measure energy intake and physical activity have a large random error; second, a possible bias in reporting energy intake because of a large body weight or an excessive weight gain cannot be discounted. In our opinion, however, a more reasonable explanation is that there is little or no relation between energy intake (even when adjusted for physical activity and lean body mass) and infant birthweight in our general population of pregnant women. The fact that lean body mass was significantly correlated with infant birthweight might be due to the positive relation between maternal birthweight and prepregnancy weight and thus indirectly reflect the 'inheritance of birthweight' (Langhoff-Roos *et al.* 1987*b*).

Our study only concerns 'external aspects' of energy balance, namely energy intake and physical activity. A new method (doubly-labelled water) has estimated that the energy expenditure associated with physical activity in women in an industrialized country requires 1·38 times the energy needed to maintain the basal metabolic rate (Prentice *et al.* 1985). Thus, the energy expenditure due to physical activity, as measured by the actometer method in our study, probably accounts for less than one third of the total energy output. The part of the maternal fat accretion and infant birthweight not associated with 'external aspects' of the energy balance may be related to the effect of pregnancy on the resting metabolic rate, including the thermogenic response to meals.

Furthermore, there are individual differences in circulating levels of hormones, such as oestrogen, progesterone, human placental lactogen and insulin, which affect metabolism and tissue deposition. Such factors might partly explain why some pregnant women (at least in affluent societies where basic dietary needs are met), in spite of large differences in energy intake, have the same weight gain during pregnancy, and why pregnant women with the same energy intake may gain different amounts of weight. Further studies are needed to elucidate the mechanisms that regulate maternal energy metabolism during pregnancy and the way in which they are related to intrauterine growth.

Acknowledgments

This study was supported by a grant from the First of May Flower Annual Campaign for Children's Health. We wish to thank Synnove K. Jansson, RN, midwife, for her technical assistance during the study.

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Received 13 February 1987
Accepted 9 June 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol 94, pp. 1186–1191

Fertility and obstetric history in patients with familial Mediterranean fever on long-term colchicine therapy

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Summary. The obstetric histories were examined for 36 women with familial Mediterranean fever (FMF) on long-term colchicine treatment followed for periods ranging between 3 and 12 years. Seven of 28 pregnancies (25%) associated with colchicine therapy ended in miscarriage. Thirteen women (36%) had periods of infertility; these were due to ovulatory dysfunction in six women, to peritoneal adhesions in four and remained unexplained in three women. The rates for miscarriage and infertility are high but are similar to those reported for women with FMF before colchicine therapy was introduced. All 16 infants born to mothers who had taken colchicine during pregnancy were healthy. Currently, we do not advise discontinuation of colchicine before planned pregnancy but recommend amniocentesis for karyotyping and reassurance.

Familial Mediterranean fever (FMF) is manifested by short, self-limiting attacks of fever, peritonitis, pleuritis and arthritis. The disease affects mainly Jews, Armenians, Arabs and Turks. Symptoms start usually before the age of 20 years. Amyloidosis is the main complication of the disease and develops in a small percentage of patients (Ehrenfeld *et al.* 1961; Eliakim *et al.* 1981).

Continuous prophylaxis with colchicine is effective in the suppression of the attacks in most patients (Levy & Eliakim 1977). It has been shown recently that colchicine prevents both the development of amyloidosis and additional deterioration of renal function in patients with early amyloidosis (Zemer *et al.* 1986). Side-effects of colchicine given in therapeutic doses are usually minor and include abdominal pain, diarrhoea and vomiting.

Infertility has been reported in up to 30% of untreated women with FMF (Ismajovich *et al.* 1973); ovulatory dysfunction and peritoneal adhesions have been implicated.

Since the introduction of long-term preventive colchicine therapy for patients with FMF, concern has been raised for the potential development of adverse effects including those on fertility. Our initial observations (Levy & Yaffe 1978) suggested that male fertility was not affected by colchicine, but our recent observations disclosed that as many as 20% of male FMF patients on long-term colchicine therapy may develop fertility problems associated with either azoospermia or impairment of sperm penetration (Ehrenfeld *et al.* 1986). We now report our 12-year experience with 36 women with FMF who were treated with colchicine. During this period 13 women suffered periods of infertility.

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Patients and methods

A total of 84 women with FMF were followed for periods up to 12 years to investigate the effects of colchicine therapy on the disease and any side-effects. Colchicine was given prophylactically on a long-term basis at daily doses ranging between 0·5 and 2·0 mg. Fifty-eight patients were between 17 and 50 years of age at the onset of the study; 36 of these were married and they comprised the study group (Table 1). The patients were divided into three groups, according to whether or not they had received colchicine before and/or during pregnancy. Some women were considered more than once, as their pregnancies occurred under different treatment conditions. All patients were routinely instructed to discontinue colchicine therapy at least 3 months before attempting to conceive.

Results

Pregnancies

Group 1. This group included 14 women who were observed before the introduction of colchicine treatment in 1972. Thirteen women conceived and one suffered from primary infertility. All 31 pregnancies in these 13 patients terminated in normal births of healthy babies.

Group 2. This group included 31 women who were observed during colchicine therapy. Three had primary infertility and five secondary infertility. Thirteen women continued taking colchicine until pregnancy was diagnosed (subgroup a). There were 17 pregnancies in this subgroup, five of them terminated in miscarriage and five were aborted because of the possible risk associated with colchicine ingestion during the early weeks of the pregnancy. Seven healthy babies were born. Ten women (subgroup b) continued taking colchicine throughout the entire period of pregnancy. Eleven pregnancies were recorded in this subgroup, two ended in miscarriage and the other nine in the birth of healthy babies.

Group 3. This group included 25 women who had discontinued colchicine therapy before attempting to conceive. Two women had primary infertility and six secondary infertility. Seventeen women conceived; of the 24 pregnancies in this group, two ended in miscarriage and 22 ended in the birth of healthy infants.

Eight women from group 2 underwent amniocentesis; normal karyotypes were found in all cases.

Infertility

Thirteen of the 36 women with FMF (36%) had periods of infertility ranging between 2 and 15 years (Table 2). Infertility is defined as failure to achieve pregnancy despite attempts to conceive for at least 12 months. The male partners of these 13 women had normal sperm counts and no other detectable causes for infertility. Four of the 13 infertile women (31%) suffered from primary infertility and only one of them conceived subsequently (patient 3, Table 2). The other nine women (69%) had secondary infertility after one or more successful pregnancies.

Twelve of the 13 infertile women were on long-term colchicine therapy during the period of infertility. Six of them either discontinued or

Table 1. Reproductive history and outcome in 36 women with familial Mediterranean fever in relation to colchicine therapy*

	Group 1 Before colchicine (n = 14)	Group 2 Colchicine given (n = 31) (a) Until pregnancy	(b) Before and during pregnancy	Group 3 Colchicine discontinued (n = 25)
Number of women who became pregnant	13	13	10	17
Number of pregnancies	31	17	11	24
Miscarriages	No data	5	2	2
Abortions	No data	5	—	—

* Some women were observed under more than one treatment situation

Table 2. Characteristics of 13 women with familial Mediterranean fever with fertility problems

Subject no	Age at onset of colchicine therapy (years)	Obstetric history†			Infertility		Colchicine treatment during infertility period	Investigation of infertility			Treatment
		G	P	Ab	Age at onset	Duration (years)		HSG	Laparoscopy	Ovulatory function	
Primary infertility											
1	36	0	0	0	34	15	Continuous	Right tubal occlusion	Right occlusion	Anovulation	Pergonal
2*	21	0	0	0	27	3	Interrupted	Normal	NP	Anovulation	Clomid/Pergonal
3	22	2	2	0	23	6	Continuous	Normal	Normal	Normal	Artificial insemination (from husband)
4	23	0	0	0	23	6	Discontinued	Normal	Normal	Anovulation	Pergonal/Clomid
Secondary infertility											
5	21	2	1	1	25	3	Continuous	Normal	Normal	Normal	None
6	24	3	2	1	27	4	Interrupted	Normal	Normal	Anovulation	Clomid + Pergonal
7	32	6	5	1	35	4	Discontinued	Bilateral occlusion	NP	Normal	None
8	28	2	2	0	28	4	Continuous	Normal	NP	Anovulation	Clomid
9	26	1	1	0	26	5	Continuous	Suspected pelvic adhesions	Mild pelvic adhesions	Normal	None
10	31	2	2	0	30	5	Interrupted	Suspected pelvic adhesions	Severe pelvic adhesions. Both tubes patent	Normal	Tuboplasty planned
11*	20	1	1	0	22	5	Continuous	Suspected pelvic adhesions	Severe pelvic adhesions Laparotomy: multiple ovarian cysts	Normal	Adhesionalysis in laparotomy
12	26	3	2	1	27	9	Interrupted	Right tubal occlusion	Right tubal occlusion. No adhesions	Normal	Pergonal trial
13	18	2	1	1	22	3	None	Normal	NP	Anovulation	None

* Amyloidosis

† G, Gravida; P, para; Ab, abortus.

NP, Not performed.

had temporarily interrupted colchicine treatment for periods ranging between 1 and 4 years, but nevertheless failed to achieve pregnancy. Customary procedures such as basal body temperature recording, mid-luteal progesterone determinations, cervical mucus analysis, hysterosalpingography and, if indicated, laparoscopy were performed. The cause of infertility could be determined in 10 (77%) of the 13 women. In six, anovulation or ovulatory dysfunction was found and four women had various degrees of pelvic adhesions or tubal disease which could have contributed to infertility. In the remaining three women, no cause could be detected in spite of thorough investigations.

Three of 36 women in the study group had amyloidosis; one of them suffered from primary infertility, another from secondary infertility and the third was advised to avoid pregnancy because of severe renal failure.

Discussion

Concern about adverse effects of long-term administration of colchicine in man stems from the fact that this drug interacts with microtubules and is a well-known mitotic inhibitor destroying germ cells in animals, although the doses used in most animal experiments were 30–50 times higher than conventional doses used in gout or FMF (Bremner & Paulsen 1976). Two children with Down's syndrome were born to patients with gout on continuous colchicine treatment (Ferreira & Buoniconti 1968), but patients with gouty arthritis are relatively old, thereby having an increased risk of trisomy. Retrospective studies of gouty patients on maintenance colchicine for 5–20 years did not detect problems related to fertility or teratogenicity (Yu 1982). Obviously, the number of female patients in that series was small.

During the last 13 years colchicine has become the recommended treatment for FMF. This disease occurs in patients of child-bearing age and affects men and women equally. Experience with maintenance colchicine treatment in FMF patients and its effect on female fertility and teratogenicity is limited. Cohen *et al.* (1977) in a cytogenetic study of 38 FMF patients on colchicine therapy did not detect any important changes in their lymphocyte chromosomes nor in mitotic rates, tetraploidy or chromosomal damage.

The prevalence of infertility among married couples in Israel has been reported by Dor *et al.* (1977) to be 10–15%. Male factors are responsible in 30–40% of these cases. Of the 36 women in our study 13 (36%) experienced periods of infertility, male factors were excluded in all cases. Before colchicine therapy was introduced, Ehrenfeld & Polishuk (1970) reported infertility in one of seven women with FMF and Ismajovich *et al.* (1973) found primary infertility in 15 out of 45 women (30%) with FMF which was considered to be due to ovulatory dysfunction in 87%.

It was assumed previously that peritoneal adhesions due to recurrent peritonitis were the main cause of infertility in women with FMF (Ehrenfeld & Polishuk 1970). In the present series, obvious peritoneal or pelvic adhesions were found in only 4 of the 13 women who complained of infertility. This rate is similar to that expected in the general population.

In contrast to Ismajovich *et al.* (1973) we found ovulatory disturbances in only 46% (6 of 13) of the infertile women in our study. The rate of ovulatory dysfunction as the cause of infertility in the general population in Israel has been reported to be 31% (Dor *et al.* 1977).

In three of 13 infertile women (23%), the cause of infertility could not be identified in spite of intensive diagnostic efforts. The reported rate of unexplained infertility in the general population ranges from 6% to 27% (Moghissi & Wallach 1983).

Matzner & Brzezinski (1984) have recently demonstrated that the peritoneal fluid of women with FMF lacks an inhibitor of neutrophil chemotaxis (C5a) and that the C5a inhibitor deficiency may have a role in the pathogenesis of the inflammatory attacks. The possibility that increased neutrophil chemotaxis has an adverse effect on sperm–egg interaction at the ampula of the oviduct should be further investigated. Altogether there is no clear evidence that colchicine has adverse effects on fertility in women with FMF. Twenty-two women had no fertility problems in spite of prolonged colchicine therapy. Cessation of treatment for long periods of time (2–5 years) had no apparent influence on infertility in six out of 13 women. Furthermore, colchicine has been reported to reduce the formation of peritoneal adhesions (Granat *et al.* 1983). The relatively low prevalence of obvious peritoneal adhesions in our patients may possibly be related to the effect of this drug.

In this study, the prevalence of miscarriage in women who conceived while on colchicine treatment was relatively high (25%). Ehrenfeld & Polishuk (1970) calculated a fetal wastage of 30% in 15 pregnancies in untreated FMF patients, where four terminated in miscarriage and one in tubal pregnancy. Thus the prevalence of miscarriage in women with FMF appears to be greater than that in the general population irrespective of colchicine therapy.

Zemer *et al.* (1980) reported 76 full-term pregnancies occurring while one of the parents was on daily colchicine prophylaxis (the mother in 52 cases and the father in 24). Two women with primary infertility of 10 and 13 years' duration conceived only after colchicine therapy which had induced remission of inflammatory attacks. Virtually all pregnancies were unplanned and contrary to advice. Most women stopped taking colchicine when pregnancy was diagnosed, but three continued taking the drug to term. Of the 76 pregnancies 75 terminated in the birth of normal infants and one woman gave birth to a child with Down's syndrome. She had conceived while on colchicine and discontinued the drug 1 month after pregnancy was diagnosed. A later pregnancy in this woman, also while on colchicine, terminated in the birth of a normal child. These authors also noted the occurrence of early miscarriage after cessation of colchicine. Based on their experience, Zemer *et al.* (1980) recommended amniocentesis in all pregnancies associated with colchicine therapy, although in their series of 21 amniocenteses up to 1980 none showed abnormalities. Pras *et al.* (1984) reviewed 55 pregnancies associated with colchicine therapy between 1977 and 1982. One pregnancy was aborted after amniocentesis detected a fetus with trisomy 23. All the other pregnancies resulted in the births of healthy infants.

Of special concern is the problem of pregnancy in patients with renal amyloidosis, since it results in either abortion, stillbirth or deterioration of renal function. Although there is not sufficient information available on this problem, it seems at present that patients with amyloidosis should be advised not to conceive (Pennington & Pfanner 1973; Cabili *et al.* 1985).

In summary, colchicine therapy does not seem to add to the underlying obstetric risk of women with FMF. We currently do not advise our patients to discontinue therapy for the purpose of pregnancy but recommend that once they become pregnant, amniocentesis be performed for reassurance and karyotyping.

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Received 24 September 1986
Accepted 15 April 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1192–1198

Effects of subcutaneous oestradiol implants on ovarian activity

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Summary. The effects of subcutaneous oestradiol implants on ovarian activity were investigated in 14 ovulating premenopausal women. Treatment with either 100 mg or 150 mg oestradiol was combined with cyclical oral norethisterone from days 20 to 26 of the cycle to ensure regular withdrawal periods and prevent endometrial hyperplasia. Ovarian function was monitored by regular pelvic ultrasonography and urinalysis over a period of nine cycles. During the first three cycles after hormone implantation, follicular development continued in almost half the study group, but only one of the women in each treatment group showed signs of follicular rupture and luteinization. By the sixth cycle, over half the women given the lower dose of oestradiol were developing follicles, including a large functional cyst in one, but none of them ovulated. A further implant given early in the seventh cycle was associated with ovarian suppression in all cases. Both doses of implant elevated the excretion of oestrone-3-glucuronide compared to pretreatment. The contraceptive and therapeutic implications of these results are discussed.

Subcutaneous implants of crystalline oestradiol are an established form of hormone replacement therapy for the climacteric (Studd *et al.* 1977; Brincat *et al.* 1984). Although the alleviation of menopausal symptoms and the prevention of osteoporosis are at present the major indications for the use of natural oestrogens, including oestradiol implants, there is increasing evidence that premenopausal women may also benefit from this form of treatment. Since the pioneering work of Greenblatt & Suran (1949), who employed pellets of oestradiol for conditions such as acne and hirsutism as well as the climacteric syndrome, we have also shown that these implants are an effective treatment for menstrual migraine (Magos *et al.* 1983) and the premenstrual syndrome (Magos *et al.* 1986).

This approach to the management of these cyclical conditions suppresses the hypothalamic-pituitary-ovarian axis and so reduces the magnitude of the many physical, psychological and behavioural variables that normally fluctuate in phase with the ovarian cycle, and in some way mediate the above disorders (Magos & Studd 1985). Oestradiol implants were first shown to suppress ovulation by Emperaire & Greenblatt (1969), who also observed the contraceptive efficacy of a combination of implants and cyclical progestogen, the latter given to induce regular withdrawal periods. Employing a step-down regimen of 100 to 25 mg oestradiol given at 6-month intervals, their series was later extended to a total of 7099 cycles. There were only five pregnancies: four within 6 months of the first implant of 100 mg (Greenblatt *et al.*

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1977), and one during the maintenance dose of 25 mg oestradiol (Greenblatt *et al.* 1979). The authors therefore recommended that alternative methods of birth control should be used for at least the first cycle after the start of hormone implantation, although two of the four early conceptions occurred after that time.

Both from contraceptive and therapeutic aspects, it is important to know the dynamics of ovarian suppression after oestradiol implants. The present study was designed to determine the early effects of two doses of oestradiol implants on ovarian activity using intensive ultrasound and biochemical monitoring.

Patients and methods

The study included 14 women referred to the PMS Clinic at Dulwich Hospital with symptoms of premenstrual syndrome (11 patients) and menstrual migraine (3 patients). They were chosen because they had regular menstrual cycles (28±2 days), proven fertility, intact ovaries and were willing to have regular ultrasonic and biochemical monitoring for a period of nine menstrual cycles. The women were otherwise healthy, of normal weight and were not taking any regular medication, including agents that influence ovarian function. All had been either sterilized or were using non-hormonal contraception which they were advised to continue throughout the study. The mean age of the study group was 36·4 years (range 27–49).

After a control cycle of investigations (described below) to ensure that ovulation had taken place, all subjects were treated with subcutaneous oestradiol implants (Organon Laboratories). Doses of 100 mg (10 patients) and 150 mg (4 patients) were inserted under the skin of the lower anterior abdominal wall according to the method described by Thom & Studd (1980). The lower dose (100 mg) was identical to the starting anovulatory implant described by Emperaire & Greenblatt (1969), while the higher dose (150 mg) was chosen as one that might suppress ovarian function more effectively. All implants were inserted within the first 5 days of the menstrual cycle. Treatment was combined with cyclical oral norethisterone, 5 mg, taken from day 20 to 26 inclusive of the menstrual cycle.

In all but one patient, the implants were repeated after six cycles; the exception was a 29-year-old woman with symptoms of severe premenstrual syndrome, who was still ovulating (and symptomatic) 3 months after the initial 100 mg implant of oestradiol, and who for therapeutic reasons was given a further implant at that time. Each patient was monitored for a total of nine cycles (one pretreatment and eight post-treatment).

Ovarian ultrasound

The women were investigated by pelvic ultrasonography twice a week (every 3–4 days) throughout the duration of the study, the interval being a compromise between the known rate of growth of pre-ovulatory follicles (Queenan *et al.* 1980) and patient acceptability. Scans were performed by the same observer (A.L.M.) with a Technicare Autosector AM10479 real-time sector scanner and a 3·5 MHz probe. Using the full bladder technique described by Donald (1963), both ovaries were displayed and the mean diameter of any follicles determined from measurements taken in the transverse, longitudinal and sagittal planes. Changes consistent with ovulation such as the appearance of internal echoes, and collapse and disappearance of the follicles were also noted (Hackeloer & Sallam 1983).

Urine biochemistry

Early morning urine (EMU) was collected daily by all women and stored at −20°C until assayed. The concentration of oestrone-3-glucuronide (El-3-G) was measured on alternate day samples before and after hormone implantation using a solid phase chemiluminescence immunoassay (CIA) as described by Weerasekera *et al.* (1982). The concentration of pregnanediol-3alpha-glucuronide (Pd-3alpha-G) was also determined by CIA from the EMU samples collected on menstrual cycle days 9/10 and 19/20 (immediately preceding medication with the oral progestogen) according to the method of Eshhar *et al.* (1981). El-3-G and Pd-3alpha-G are major urinary metabolites of plasma oestradiol and progesterone respectively, and the concentrations in EMU have been shown to correlate well with the levels of the parent hormone in peripheral venous plasma (Collins *et al.* 1981).

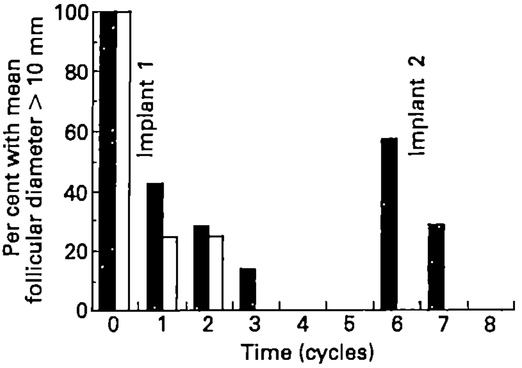

Fig. 1. Follicular growth before and after treatment with oestradiol implants. ▨, 100 mg ($n = 7$); □, 150 mg ($n = 4$)

Definitions

The criteria for follicular rupture and luteinization during a particular cycle were a combination of (i) a maximum mean diameter of the dominant ovarian follicle exceeding 10 mm on ultrasound, followed by changes in its size, shape or echogenicity (Queenan *et al.* 1980), and (ii) at least a four-fold increase in the concentration of Pd-3alpha-G in EMU between days 9/10 and 19/20 (Collins *et al.* 1981). The ultrasound criterion of 10 mm might be thought to reduce the specificity of the results, but it must be considered that the interval between the scans was 3–4 days and the findings of Watts *et al.* (1985), that women with the premenstrual syndrome tend to develop smaller follicles and ovulate earlier in the cycle than asymptomatic controls, should also be borne in mind.

Ovarian cyclicity was confirmed by the detection of mid-cycle and mid-luteal peaks of El-3-G excretion (Collins *et al.* 1979).

Results

Although all 14 women were monitored during the study period, the intensive, varied and prolonged protocol was associated with inconsistencies in patient compliance. Thus, three of the ten patients receiving 100 mg oestradiol implants, while providing the necessary EMU samples, proved unable to attend regularly enough for pelvic scans and have therefore been excluded from the ultrasound findings. Also, two women from each treatment group failed to collect sufficient daily EMU specimens for meaningful El-3-G analysis in the latter half of the study. Therefore, El-3-G was not assayed after the first three cycles of treatment in the group given 150 mg oestradiol.

100 mg oestradiol

There was continued development of follicles larger than 10 mm in diamater in 3 of the 7 patients monitored during the first three cycles after the implant was administered (Fig. 1). Subsequently, significant follicular growth was absent until the sixth cycle. At that time, 4 of the 7 women were found to be developing follicles >10 mm in diameter, including one who had a functional cyst measuring 51 mm. Follicular activity continued in two of the group immediately after the second implant given early in the seventh treatment cycle, but not thereafter (Fig. 1). The single large cyst regressed spontaneously.

Despite the follicular appearances, only one woman had ultrasonic and biochemical evidence of both follicular rupture and luteinization, ovulation having taken place during the second and third cycles after the start of treatment (Fig. 2). As noted earlier, this woman was given a further 100 mg oestradiol implant at this stage which effectively suppressed further ovarian activity. The mean EMU Pd-3alpha-G concentrations are shown in Fig. 3, the data being combined from both treatment groups.

The effect of treatment on the typical ovulatory pattern of EMU El-3-G excretion obtained during the control cycle was two-fold. First, the absolute concentration of El-3-G was consistently increased such that only the ovulatory peak seen during the pretreatment cycle resulted in higher levels. This effect was maximal immediately after implantation and gradually waned

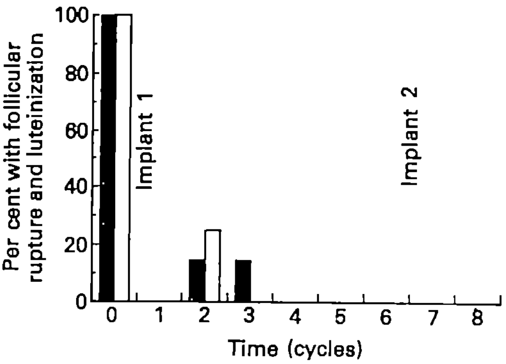

Fig. 2. Follicular rupture and luteinization before and after treatment with oestradiol implants ■, 100 mg ($n = 7$); □, 150 mg ($n = 4$)

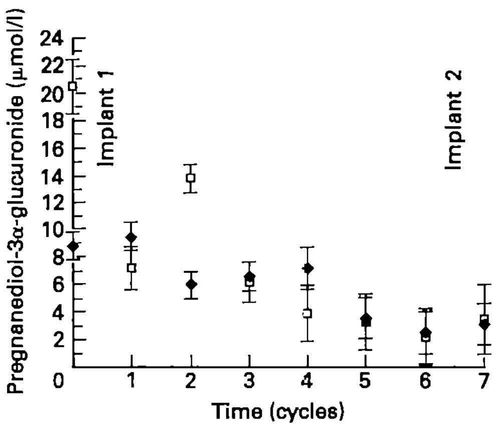

Fig. 3. The geometric mean (±SE) concentrations of pregnanediol-3alpha-glucuronide in early morning urine before and after treatment with oestradiol implants. Data amalgamated from both treatment groups. □, Day 10 ($n = 14$); ◆, day 20 ($n = 14$).

until the next implant was inserted (Fig. 4). Second, the day-to-day fluctuation of the metabolite was reduced, this effect also being maximal during the first cycle but still apparent during the sixth cycle (Fig. 4).

150 mg oestradiol

Although there were fewer subjects in this group, the results were basically similar. Significant follicular activity was present during the first two cycles after treatment in one of the four women scanned, but not thereafter (Fig. 1). Of these two episodes, follicular rupture and luteinization appeared to have taken place only during the second cycle (Fig. 2). As with the lower dose of oestradiol, the mean concentration of El-3-G in the EMU specimens was again consistently higher than in the control cycle, but still within the normal physiological range (Fig. 5). In contrast to the 100 mg implant, however, the short-term fluctuation of the metabolite was not reduced; this finding probably reflects the small numbers studied.

Discussion

Ovulation can only be proven to have occurred when either an ovum is detected in the female genital tract or conception has taken place. Our results provide only circumstantial evidence for the presence or absence of ovulation following treatment with oetradiol implants. Within these limitations, it appears from the present study that ovarian activity continues for at least three cycles after the start of treatment with 100 mg oestradiol implants, including evidence of follicular rupture and luteinization in some women during this time. Follicular development recommences by the sixth cycle, at the time of falling urinary oestrogen concentrations, but without the evidence of ovulation. This pattern of implant action is consistent with the hormonal data obtained from postmenopausal women by Thom *et al.* (1981). Ovarian function was not completely suppressed by the larger dose of oestradiol, despite the associated higher concentrations of the oestradiol metabolite, El-3-G, in EMU samples. The results of treatment with 100 mg oestradiol implants are in accord with the data presented by Greenblatt *et al.* (1977), who of course obtained absolute proof of ovulation by the pregnancies that occurred.

The reason for the universal absence of ovulation during the first cycle of treatment in contrast to the subsequent two cycles is unclear. Data presented by Greenblatt *et al.* (1977) suggested that the timing of implantation was critical; insertion early in the ovarian cycle, as in our study, tended to suppress ovulation immediately, whereas later treatment delayed the anovulatory effect until the next cycle. The absorption of implants follows an exponential pattern being fast early and progressively slowing (Greenblatt & Hair 1945). The peak oestrogen levels observed during the first cycle may disrupt the normal pituitary feedback loops and thus the mid-cycle surge of LH. Equally, the immediate findings might be a quirk of the small number of subjects investigated. Only a more

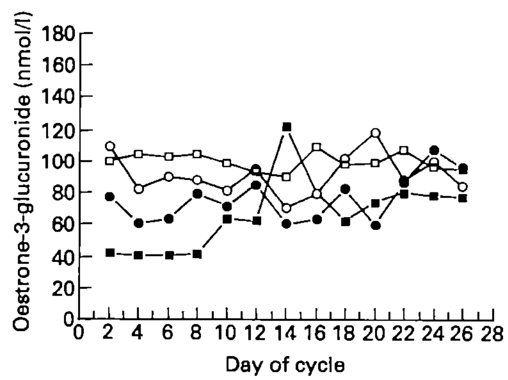

Fig. 4. The geometric mean concentrations of oestrone-3-glucuronide in early morning urine during menstrual cycles before and after treatment with 100 mg oestradiol implants. Data expressed relative to the start of menstruation. ■, Control cycle; □, first cycle; ○, third cycle; ●, sixth cycle.

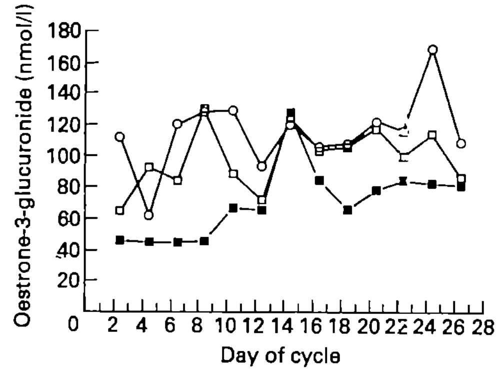

Fig. 5. The geometric mean concentrations of oestrone-3-glucuronide in early morning urine during the menstrual cycle before and after treatment with 150 mg oestradiol implants. Analysis limited to the first half of the study. Data expressed relative to the start of menstruation ■, Control cycle; □, first cycle, ○, third cycle.

extensive study with detailed analysis of gonadotrophin secretion could resolve the issue. Certainly, in postmenopausal women plasma gonadotrophins are suppressed to premenopausal levels within 1–2 months of the start of implant therapy (Thom *et al.* 1981).

For comparison, the ovarian effects of oral natural oestrogens have also been investigated. Greenblatt *et al.* (1954) reported on a step-down regimen of conjugated equine oestrogens showing that a starting dose of up to 7·5 mg daily was required to inhibit ovulation. This is 6–12 times the usual postmenopausal replacement dose, and may not be well tolerated by asymptomatic women taking the hormone for contraception. In contrast, subcutaneous implants of oestradiol, initially at a dose that is only twice the usual replacement dose, is an effective anovulatory agent.

This difference in potency is explained by three factors. First, oestradiol is a much more active oestrogen than oestrone, the principal constituent of equine oestrogens. Second, subcutaneous administration bypasses the gastrointestinal tract where oestradiol is preferentially converted to oestrone (Ryan & Engel 1953). Third, the portal circulation and 'first pass' effect on liver metabolism is similarly avoided, whereby oral oestrogens are largely metabolized and inactivated before reaching the systemic circulation (Whitehead 1985). Apart from potency, these pharmacodynamic differences confer other advantages on non-oral therapy including avoidance of bolus absorption (Lyrenas *et al.* 1981), maintenance of normal follicular ratio of plasma oestradiol to oestrone levels as shown here and elsewhere (Thom *et al.* 1981), and minimal effects on the hepatic metabolism of macromolecules such as renin substrate and antithrombin III, substances implicated in the development of hypertension and venous thrombosis with oral therapy (Elkik *et al.* 1982).

Although large scale epidemiological data are not available, 'natural' oestradiol implants also offer considerable theoretical advantages over the commonly used 'synthetic' oestrogens by their relative lack of effect on the clotting and fibrinolytic systems (Thom *et al.* 1978). Similarly, the hypertensive action of the combined pill, related at least in part to the dose of the progestogenic component, has been found to be absent with hormone therapy identical to the regimen used in this study (Greenblatt *et al.* 1977). Nonetheless, the safety of the regimen used in this study could be further improved by the substitution of a non-androgenic progestogen for norethisterone that would be administered for 12 days per cycle, thereby avoiding both adverse lipid changes and endometrial hyperplasia (Hirvonen *et al.* 1981; Paterson *et al.* 1980). As for other anovulatory agents, the published data suggest that oestradiol implants and cyclical oral progestogen are better tolerated than danazol, while treatment is not complicated by hypo-oestrogenaemia associated with LH-RH agonists (Magos *et al.* 1984).

The above considerations make subcutaneous oestradiol implants combined with cyclical oral progestogen an attractive alternative to other anovulatory therapies, particularly in the years approaching the menopause. Indications may include contraception and the management of those disorders that appear to be influenced by the ovarian cycle (Magos & Studd 1985). The full potential of anovulatory therapy as an adjunct to conventional treatments for conditions as diverse as diabetes mellitus, epilepsy and rheumatoid arthritis remains to be exploited, but it is noteworthy that the combined oral contraceptive has been reported to improve diabetic control (Sandstrom 1969), to treat catamenial epilepsy (Rossi & Goplerud 1974), and to reduce the risk of rheumatoid arthritis (Linos *et al.* 1983).

Acknowledgments

We would like to thank the Department of Radiology, Dulwich Hospital, for the use of their sector scanner.

The work was supported by a grant from King's Voluntary Research Trust.

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Received 5 November 1986
Accepted 16 May 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1199–1204

Effect of nomegestrol acetate, a new 19-nor-progesterone derivative, on pituitary-ovarian function in women

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Summary. After two control cycles, 13 normally menstruating women were treated from day 5 to 25 of the third consecutive cycle with nomegestrol acetate (NOM Ac) 1·25, 2·5 or 5 mg once a day. Plasma oestradiol, FSH and LH concentrations were assayed daily from day 5 to day 25 and plasma progesterone concentrations from day 12 to day 25. Ovulation was inhibited in every woman; LH and progesterone levels were uniformly depressed. With 5 and 2·5 mg/day, plasma oestradiol remained low with high FSH values. With 1·25 mg/day, oestradiol concentrations reached levels similar to those achieved during the control follicular phase, with a concomitant decrease in FSH secretion. These results show an hypothalamic-pituitary effect and suggest an ovarian action, both responsible for a potentially useful contraceptive property.

The inhibitory effect of synthetic progestogens on gonadotrophin secretion depends on their chemical structure. Potent for the 19-nor-testosterone derivatives (Larsson-Cohn *et al.* 1970; Eckstein *et al.* 1972; Friedrich *et al.* 1975; Viinikka *et al.* 1977; Johannisson *et al.* 1982; Kopera & Weijers 1983), the anti-gonadotrophin property is inconstant among 17-OH-progesterone-derived compounds (Diczfalusy *et al.* 1969; Jaffe *et al.* 1969: Franchimont *et al.* 1970; Neumann 1978). Lately, 19-nor-progesterone derivatives were found to exert a marked inhibitory effect on ovulation (Lahteenmaki *et al.* 1981; Rozenbaum 1984; van der Linden *et al.* 1985).

The action of progestogens on ovarian and pituitary functions also depends on dosage regimen and duration. When progestogens are given continuously at low doses, the ovulation inhibition is inconstant and peripheral mechanisms are responsible for the contraceptive effect (Rudel *et al.* 1965; Kuttenn *et al.* 1978; Diczfalusy & Landgren 1983); under this type of treatment, when the cycle is anovulatory, a hyper-oestrogenic state frequently takes place due to uninterrupted follicular maturation (Larsson-Cohn *et al.* 1970; Friedrich *et al.* 1975). At higher doses, anovulation is the rule: for example the fickle antiovulatory effect of 5 mg/day of medroxyprogesterone acetate becomes regular at 10 mg/day (Wikstrom *et al.* 1984). The gonado-pituitary suppression is also observed when progestogens are administered 15–20 days during the menstrual cycle. LH, FSH and oestradiol secretions are impaired by lynestrenol, 5 or 10 mg daily from day 10 to day 26 (Borglin 1964; Kaiser 1964; Dargent *et al.*

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1978). Ovulation is inhibited by ORG 2969 (17-alpha-ethinyl-18-methyl-11-methylene-4-oestrene-17-beta-ol) 60 μg daily from day 1 to day 20 (Skouby 1976; Viinikka *et al.* 1976) or by the 19-nor-progesterone derivative, promegestone, 250 μg daily from day 5 to day 24 (van der Linden *et al.* 1985).

Nomegestrol acetate (NOM Ac) is an orally active 19-nor-progesterone derived progestogen, the gonado-pituitary suppressive action of which has previously been described in animals (Paris *et al.* 1983; Thevenot 1984). The aim of this study was to describe the dose-related changes in the hormonal profiles of normally menstruating women with daily oral administration of NOM Ac from day 5 to day 25.

Patients and methods

Patients

The investigation involved 13 healthy volunteer women who had no previous history of gynaecological or endocrine disorders. Their mean age was 34 years (range 25–42), and their mean body weight 55·2 kg (range 48–65). They had not received any hormonal treatment for at least 3 months before the study.

Consecutively, two control and one treated cycle were monitored. During the first cycle, the daily basal temperature and the occurrence and duration of menses were noted. The cycle was considered normal if it lasted 25 to 30 days and if the temperature curve was biphasic. During the second cycle, basal body temperature was still recorded and blood samples were drawn each day from day 5 to day 25 to assay FSH, LH and oestradiol plasma concentrations. Progesterone was measured from day 12 to day 25. The cycle was considered normal if the following requirements were met: mid-cycle LH peak, synchronous LH and FSH peaks, oestradiol level >400 pmol/l the day before LH peak and progesterone level >16 nmol/l for 3 to 5 days (Viinikka *et al.* 1977; Landgren & Diczfalusy 1980; Lahteenmaki *et al.* 1981; Thomas *et al.* 1986). The women were given NOM Ac from day 5 to day 25 of the third cycle, one capsule daily at bedtime. Three subjects received 1·25 mg/day, five 2·5 mg/day and five 5 mg/day. LH, FSH, oestradiol and progesterone levels and basal body temperatures were recorded as for the second control cycle.

Radioimmunoassays

Blood samples were immediately centrifuged and plasma frozen and stored at −20 °C. The Fondation de Recherches en Hormonologie took care of the assays according to established procedures (Castanier & Scholler 1970; Roger *et al.* 1975; Teck Tea *et al.* 1975).

Statistics

The areas under curve (AUC) for LH and for oestradiol were compared between the different doses of NOM Ac using analysis of variance.

Results

The lapse between the time of first capsule intake and the rise in body temperature was dose-related: 1·6 days with 5 mg/day, 3·3 days with 2·5 mg/day, and 6·4 days with 1·25 mg/day. Spotting occurred in 8 women: 2 of the 5 with 5 mg/day, 4 of the 5 with 2·5 mg/day and 2 of the 3 with 1·25 mg/day.

The hormonal profiles before and during treatment are presented in Fig. 1. Mid-cycle FSH and LH surges were missing in all treated women, whichever dose of NOM Ac was used. Plasma LH concentrations were unchanged from the postovulatory values of the previous control cycle. With 2·5 mg/day and 5 mg/day, plasma FSH remained at a high level, similar to the FSH values of the control early follicular phase, throughout the treatment. With 1·25 mg/day there was a progressive decrease in the FSH plasma levels throughout the cycle. The AUC obtained with 1·25 mg/day was significantly lower than with 2·5 or 5 mg/day ($P = 0{\cdot}05$). The LH/FSH ratio was between 0·5 and 0·8 with the two higher doses whereas it rose rapidly above 1 (1–1·4) with the smallest dose.

With NOM Ac, plasma progesterone levels never exceeded 5 nmol/l at any dose, but the pattern of oestradiol secretion showed dose-dependent variations. With 5 and 2·5 mg/day, oestradiol plasma levels remained constantly below 350 pmol/l in 9 of the 10 women. In one woman, the oestradiol concentration reached 720 pmol/l on the fifth day of treatment and then decreased to very low levels (40–80 pmol/l). In women receiving NOM Ac 1·25 mg/day, there was a progressive rise in plasma oestradiol levels during the first 10 days of treatment up to values within the range of the pre-ovulatory peak of

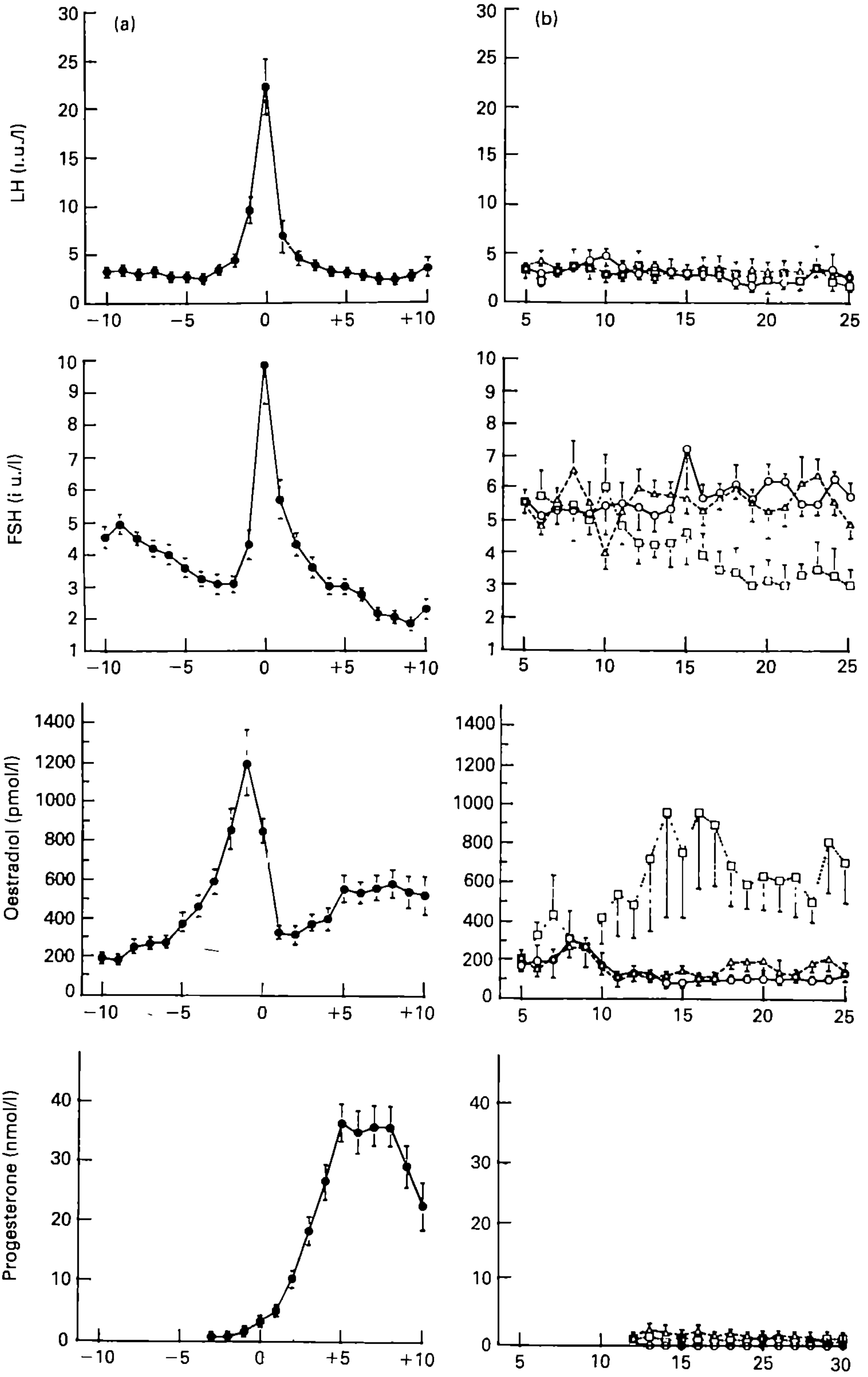

Fig. 1. Hormonal profiles before and during treatment. Column (a) shows the mean ± SEM hormone concentrations before treatment in 13 women (the LH peak is taken as day 0). Column (b) shows the hormone concentrations during the 21 days of treatment beginning on day 5 after the end of the control cycle. Three doses of nomegestrol acetate were tested: □, 1·25 mg/day ($n = 3$); △, 2·5 mg/day ($n = 5$); ○, 5 mg/day ($n = 5$).

oestradiol observed in the control cycles; thereafter, oestradiol concentrations varied between 600 and 1000 pmol/l. Consequently, the AUC measured with 1·25 mg/day was significantly greater than with the two higher doses ($P = 0{\cdot}001$).

Discussion

In this kind of study, the recruitment of women whose menstrual cycles are rigorously normal is a prerequisite (Viinikka *et al.* 1976; Landgren & Diczfalusy 1980). Stringent conditions were set and strictly adhered to. In this respect, the 16 nmol/l progesterone threshold was passed for 5 days or more by 11 women, and for 3 days by the other two women.

In all the 13 patients, NOM Ac given from day 5 to day 25 at either 5, 2·5 or 1·25 mg/day abolished the mid-cycle surge of both LH and FSH and totally prevented the production of progesterone, which indicated the inhibition of the ovulation. Whichever dose of NOM Ac was used, LH concentrations remained low throughout treatment, but not as low as with other progestogens (Dargent *et al.* 1978).

Concerning FSH and oestradiol levels, differences were observed between the effects of 5 or 2·5 mg/day, and of 1·25 mg/day. The ovarian and pituitary blockade was similar with the two higher doses; the very low oestradiol levels attested to the absence of follicular maturation despite an elevated plasma FSH. This observation may reflect a direct effect of NOM Ac on the ovary, as proposed for other progestational agents (Thiery *et al.* 1976; Mishell *et al.* 1977; Lahteenmaki & Lahteenmaki 1985), but progesterone and some progestogens have been shown to inhibit oestrogen synthesis (Schreiber *et al.* 1980; Fortune & Vincent 1983). Furthermore, folliculogenesis inhibition is associated with a decrease in LH/FSH ratio which mainly depends on the LH-RH pulse frequency (Wildt *et al.* 1981). Since such a lowered LH/FSH ratio has been observed with the two higher doses, the hypothalamus stands as another putative target of NOM Ac.

Treatment with NOM Ac, 1·25 mg/day, blocks ovulation, but oestradiol concentrations are increased as a result of unimpaired follicular maturation; the same observation has been reported with other progestogens used at low doses which were still effective in inhibiting ovulation (Larsson-Cohn *et al.* 1970; Friedrich *et al.* 1975; Viinikka *et al.* 1977; Landgren & Diczfalusy 1980). The increase in oestradiol levels is associated with a decrease in plasma FSH. The absence of a gonadotrophin surge, despite elevated oestradiol levels during the follicular phase, indicates that the positive feedback of oestradiol on gonadotrophins is disrupted. Such a mechanism has previously been reported for ST 1435 (Lahteenmaki & Lahteenmaki) and other progestogens (Weiner *et al.* 1976; Ortiz *et al.* 1977).

Taken altogether, the results of this study show that NOM Ac exerts a potent antiovulatory effect, which probably acts at the hypothalamic-pituitary level but also on the ovary. This property suggests the use of NOM Ac as a contraceptive agent, especially if one considers the lack of androgenic and metabolic side-effects that can be hoped for with the 19-nor-progesterone-derived family of progestogens (Rozenbaum 1986) to which NOM Ac belongs. Further studies are currently being conducted to elucidate its mechanism of action on the follicle and on the hypothalamic-pituitary function.

Acknowledgments

We thank Dr M. Roger from the Fondation de Recherches en Hormonologie for the completion of the plasma assays, and Dr J. P. Thebaut for his supervision of the clinical study.

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Received 2 February 1987
Accepted 4 April 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1205–1211

Cisplatin, vincristine, methotrexate and bleomycin (POMB) as initial or palliative chemotherapy for carcinoma of the cervix

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Summary. Chemotherapy was given as initial therapy to 12 women with very advanced squamous cell carcinoma of the cervix and to 19 women with recurrent disease. They received a median of four courses of POMB which comprised vincristine 1·0 mg/m^2 and methotrexate 300 mg/m^2 followed by folinic acid rescue, bleomycin 30 mg as a 48-h infusion or intramuscular injection and cisplatin 100 mg/m^2 as a 12-h infusion. Two of the 14 assessable patients with recurrent disease (14%) had a complete response with no disease found histologically in one, and seven (50%) had a partial response. Although the actuarial median survival of all 19 patients with recurrent disease was 8 months, five patients have remained free from tumour progression for a median of 17 months from start of chemotherapy. Six of the 10 assessable patients receiving initial chemotherapy (60%) had a complete response (confirmed histologically in two) and two (20%) had a partial response. Nine patients had additional treatment with radiotherapy and or surgery. Although only four of the patients remain disease-free at 61, 51, 7 and 4 months, all but two were initially FIGO stage IV. Although cisplatin-induced emesis is controllable and the side-effects of methotrexate can be avoided, the POMB regimen remains potentially toxic. The small number of patients with very advanced disease who are long-term survivors prompts us to study further the role of aggressive chemotherapy as the initial treatment of patients with visceral or nodal involvement from carcinoma of the cervix.

Despite radical surgery or radiotherapy or both, over 65% of patients with FIGO stage III or IV carcinoma of the cervix will die from their disease within 5 years (Kottmeir 1985). A disappointing 5-year survival rate of only about 50% can also be predicted by histopathological staging from a subgroup of patients with stage I and II disease (Gauthier *et al.* 1985; Bichel & Jakobsen 1985). Radiosensitizers have been used to try and improve this situation. Although misonidazole has not shown any benefit there is a suggestion that hydroxyurea, given during radiotherapy, might improve survival at least in those patients with stage II disease (Piver *et al.*

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1983; Medical Research Council 1984; Stehman *et al.* 1986).

Another approach is the investigation of chemotherapy as a third type of treatment. Response rates of between 15 and 40% have been obtained with several single agents including cisplatinum, ifosfamide, methotrexate, vincristine, mitomycin C and bleomycin in patients with recurrent disease (Wasserman *et al.* 1975; Muscato *et al.* 1982; Bonomi *et al.* 1985; Blackledge *et al.* 1986). This study assessed whether a combination of four of the most active agents leads to a higher response rate as suggested by other studies (Rosenthal *et al.* 1983; Friedlander *et al.* 1983) and more importantly whether some of these responses are durable. We also assessed the effectiveness of chemotherapy given as initial treatment in patients with very advanced disease. Analysis of the factors associated with long-term survival should help to determine the optimum scheduling of chemotherapy, radiotherapy and surgery.

Patients and methods

Between June 1981 and March 1986, combination chemotherapy was given to 31 consecutive patients with squamous cell carcinoma of the cervix. Nineteen of these women (Table 1) had recurrent tumour after previous radical radiotherapy. Only one patient (no. 5) had received prior chemotherapy. Three women had received only intracavitary irradiation immediately before starting chemotherapy for extensive nodal or visceral metastatic disease (Table 2). Nine women received chemotherapy as initial treatment because of the extent of disease; seven of these women had FIGO stage IV disease (Table 2) of whom two were deemed stage IV in view of para-aortic nodal involvement demonstrated by CT scan or lymphangiogram. Seven women had lung metastases which was the only site of recurrent disease in two

The median age of the 31 patients was 45 (range 22–72) years. Before chemotherapy one

Table 1. Details of 19 patients with recurrent disease after radiotherapy

Patient no.	FIGO stage	Chemotherapy: Age at start (years)	Chemotherapy: No. of courses	Chemotherapy: Response	Further treatment	Survival from start of chemotherapy (months)
1	IIIb (N1)	39	10	CR		59 NED
2	IVb	72	2	PR		2
3	IVb	37	9	PR		9
4	IIIb	29	4	NA*		9 L
5	IVb	37	10	PR	Chest RT	18
6	IVb	61	2	NC		5
7	IIIb	45	4	CR	AX	19 NED
8	IVb (N4)	33	6	PR		17 NED
9	IVb	38	2	PR		7
10	IIIb (N1)	27	3	NA	PL	6
11	IVa	57	4	NC		10
12	IVa	62	4	NC		5
13	IIIb	57	3	NA*		9 A+D
14	IIIb	31	2	NA		4
15	IVb	69	4	PR		12 A+NP
16	IVb	60	4	PR		8 A+NP
17	IVb	32	4	PD		6
18	IIIb	50	4	PD		2 L
19	IIIb	43	2	NA		5

Abbreviations:

FIGO stage: (N1), pelvic lymph nodes or (N4), para-aortic lymph nodes involved on lymphangiogram or CT scan.

Responses. CR, complete response; PR, partial response; PD, progressive disease; NC, no change; NA, not assessable; NA*, not assessable but clinically improved.

Survival· NED, alive with no evidence of disease; A+D, alive with disease; A+NP, alive with no evidence of residual suspected tumour mass progressing; L, lost to follow-up

Further treatment: RT, radiotherapy; AX, anterior exenteration, PL, palliative lymphadenectomy.

Table 2. Details of 12 patients given initial chemotherapy

Patient no.	FIGO stage	Chemotherapy: Ages at start (years)	Chemotherapy: No. of courses	Chemotherapy: Response	Further treatment	Surgery	Survival from chemotherapy (months)
20	IV (N4)	27	5	PR	RT then Wertheim's	+	61 NED
21	IV (N4)	46	3	CR	RT then Wertheim's	−	51 NED
22	IVa	48	3	NC	RT		14
23	IV (N4)	29	4	CR	RT, surgery on relapse	+	12
24	IVb	39	5	CR	RT then suboptimal surgery	−	17
25	IIIb (N1)	48	4	CR	RT then just hysterectomy	−	21
26	IVa	46	4	NA*	RT then AX	+	10
27	IVa	22	14	PR	RT then Wertheim's	+	18
28	IVb	49	4	NC			5
29	IVa (N1)	59	4	NA*	Early death		0
30	IVb	46	3	CR			7 NED
31	IIa	46	2	CR	Wertheim's	−	5 NED

For abbreviations see Table 1.

patient (no. 24) had a performance status (World Health Organization) of 4, five patients had a performance status of 3 (nos 2, 6, 11, 16, 17) whilst remaining patients had a performance status of 0, 1 or 2.

Chemotherapy

The patients were treated with the POMB (cisplatin, vincristine, methotrexate, bleomycin) schedule as follows. On day 1 they were given a bolus injection of vincristine 1·0 mg/m^2 and methotrexate 300 mg/m^2 as a 12-h infusion in 1 litre of 0·9% sodium chloride with 15 mg folinic acid rescue at 24, 36, 48 and 60 h after the start of the methotrexate. On days 2 and 3, 30 mg of bleomycin was given as a 48-h infusion in 4 litres of 0·9% sodium chloride. After prehydration 100 mg/m^2 cisplatin was given on day 4 as a 12-h infusion in 3 litres of 0·9% sodium chloride with a total of 3 g $MgSO_4$ supplements and followed by further intravenous hydration. Two-day POMB was given to seven patients (nos 13, 16, 17, 18, 19, 29, 31) and they received their cisplatin on day 2 after 4 litres fluid prehydration and bleomycin was given by three intramuscular injections 10 mg in 1 ml of 1% lignocaine.

Treatment was repeated after a 10-day drug-free interval provided that the total white blood count was greater than 2 × 10^9/l and platelet count was greater than 100 × 10^9/l. Modifications were made to the chemotherapy given to 10 patients because of renal impairment. This consisted of a dosage reduction of cisplatin and methotrexate and prolongation of folinic acid rescue. One patient (no. 1) started chemotherapy with two courses of intra-arterial methotrexate and cisplatin and then continued with eight further courses of intravenous chemotherapy with dosages modified because of renal impairment. Another patient (27) started treatment with two courses of EMA/CO (Newlands *et al.* 1986) because she was initially thought to have choriocarcinoma.

Radiotherapy

Seven patients who received chemotherapy as their initial treatment had intracavitary irradiation soon after completing chemotherapy. These patients plus one who had initial intracavitary therapy then had external beam radiotherapy aiming to bring the pelvic wall dose up to 5500 cGy in 4–5 weeks. Three patients (nos 20, 23, 24) also had 4030–4275 cGy given to the para-aortic nodes. Radiotherapy was not given to two patients presenting with visceral metastases, or to a patient with stage IIa disease who had a Wertheim's hysterectomy after chemotherapy.

Results

Responses to chemotherapy were judged according to WHO criteria after a minimum of two courses of chemotherapy. As it is rarely possible to make accurate pelvic mass measurements clinically, the ony clinical responses accepted to fit WHO criteria were complete response, no change, or progressive disease. If there was still palpable tumour present but the only assessment of response was obvious tumour shrinkage by bimanual examination, the patient was recorded as having improvement but not WHO response.

Relapsed patients

Eight patients received four courses of chemotherapy, four received more than four courses whilst seven patients received two or three courses (Table 1). Five patients were considered not assessable, four because only bimanual measurements were available whilst in one the outline of the tumour on repeat CT scan was too indistinct to say whether a 50% volume reduction had occurred. Clinically two of these five patients were considered to have improved.

Two (14%) of the 14 assessable patients had a complete response and seven (50%) had a partial response to chemotherapy. Two patients had progressive disease during chemotherapy whilst in three patients there was no change. One of the patients classified as having progressive disease had temporary relief of symptoms. Two patients classified as no change and one classified as not assessable had relief of pelvic pain after chemotherapy.

Responses were seen in two of four patients whose interval between completion of radiotherapy and start of chemotherapy was <6 months; in two of four with an interval of 6–12 months and in four of five with intervals of >12 months. Of the six assessable patients with lung metastases, five (83%) had a partial response and one had a marginal response of their lung disease.

Survival

Three of 19 (16%) patients remain disease-free at 59+, 19+ and 17+ months from the start of chemotherapy. One of these patients had an anterior exenteration after chemotherapy as we expected recurrent tumour to be present in the indurated tissue, but none was found microscopically. Another patient who was considered a partial responder has been noted to be 'disease-free' on follow-up in another hospital. Two other responding patients, one with lung and one with liver and para-aortic metastases, have remained free of progression for 6 and 10 months after chemotherapy. All other patients have either progressive disease or have died. One 72-year-old responding patient died from cardiac failure and bronchial pnenumonia whilst myelosuppressed 27 days following her second course of reduced dose chemotherapy.

The actuarial median survival from start of chemotherapy of the nine patients obtaining a response was 22 months compared with 6 months for the five patients who had no change or progressive disease. The actuarial median survival from completion of chemotherapy of all 19 relapsed patients was 8 months.

Patients receiving initial chemotherapy

Two of 12 patients were considered not assessable. One had involvement of the bladder and clinically improved after chemotherapy. Another clinically responding patient died suddenly 13 days after her fourth course of chemotherapy and no definite cause of death was found at autopsy. Six (60%) of the 10 assessable patients had a complete response, two (20%) had a partial response and in two there was no change.

After chemotherapy eight patients received radiotherapy and six of them then had surgery. Another patient who was initially stage IIa with a bulky tumour had a Wertheim's hysterectomy with no radiotherapy. No microscopic tumour was found in this patient and in one of four other patients who had radical surgery. In retrospect, two patients had suboptimal surgery. No lymph node sampling was performed in one. Another was found to have no residual tumour in the hysterectomy specimen but dense fibrosis prevented a lymphadenectomy. She originally had involved para-aortic nodes and their removal might have prevented her relapse which occurred in that site.

Survival

Four (33%) of the patients receiving initial chemotherapy remain disease-free 61+, 51+, 7+ and 5+ months from completion of chemotherapy. Relapses have occurred in three of the six patients who had a complete response to chemotherapy and in one of two patients who had a partial response. Eight patients have died, seven due to progressive tumour. The cause of early death in one patient is unclear. The actuarial median survival from the start of chemotherapy was 17 months.

Toxicity

All patients had nausea and vomiting with the chemotherapy which has remained a problem despite the use of dexamethazone, lorezepam and high-dose metoclopramide. By omitting or reducing the dose of methotrexate and increasing the duration of folinic acid rescue in patients with renal impairment, mucositis was avoided in most patients but was still a problem in a few patients especially after the fourth course of chemotherapy. Myelosuppression was only severe in those few patients who developed mucositis and was assumed to be due to impaired methotrexate excretion. This contributed to the early death of one patient (no. 2). Alopecia was only mild in all but three patients.

Discussion

This study demonstrated a 71% overall response rate to POMB chemotherapy in 24 assessable patients with advanced carcinoma of the cervix. Using the same four drugs but different dosages and schedules, Rosenthal *et al.* (1983) recorded a 66% response rate in 15 patients with recurrent tumour. Other workers using combinations which included cisplatin and bleomycin have also reported response rates over 50% (Daghestani *et al.* 1983; Friedlander *et al.* 1983; Bloch *et al.* 1984). Apart from one study where platinum was given in a weekly intensive regimen (Piver *et al.* 1984) responses to single agent chemotherapy appear lower than when combinations are used (Bonomi *et al.* 1985; Muscato *et al.* 1982).

Although the high response rate was associated with partial or total control of tumour symptoms in all but three patients, this was at the expense of considerable toxicity and many remissions were of short duration. Unfortunately there is no way at present of predicting which patients would benefit from this aggressive chemotherapy. It is to be hoped that there will be less toxicity when cisplatin is substituted by its analogue carboplatin. This drug has already been shown to have comparable activity to cisplatin in early trials in carcinoma of the cervix (Lira Peurto *et al.* 1986).

Disease-free survival for more than 1 year after therapy of recurrent cervical carcinoma is rarely seen (Bonomi *et al.* 1985; Barber 1979). It is therefore encouraging in this study that although most patients treated for recurrent disease had only short remissions, three patients remain disease-free between 17+ and 59+ months from starting chemotherapy and two patients with visceral metastases have maintained good partial responses for 8+ and 12+ months. The chemotherapy is responsible for these prolonged survivals as only one of these three patients had additional surgery and no active tumour was found.

Four of 12 patients who received initial chemotherapy remain disease-free. This is disappointing as the response rate to chemotherapy was 80% in these patients compared with 64% in relapsed patients. However, these 12 patients, of whom 10 were stage IV, were only offered initial chemotherapy because of their adverse prognostic factors. Although there has not been a dramatic effect on survival, a randomized trial, adequately stratified for prognostic factors, is needed to see if there is a survival advantage in patients who start treatment with chemotherapy.

Four courses of POMB chemotherapy produced as high a response rate as any other regimen used in cervical cancer, yet it appears to have a low curative potential in very advanced disease. If the observation that squamous cell cancers of the head and neck that are resistant to chemotherapy are resistant to radiotherapy is true for cervical cancer (Ensley *et al.* 1984), there is a powerful case for investigating the role of radical surgery rather than radiotherapy after chemotherapy in selected early stage poor prognosis patients. The surgical complication rate should be lower if there has been no previous radiotherapy (Blake *et al.* 1984).

It is unclear from the present study whether the few long-term survivors benefited from surgery in addition to radiotherapy. Four of the six patients who had optimal surgery within 10 weeks of radiotherapy and or chemotherapy are currently disease-free and although three of them had no microscopic evidence of disease this could not have been predicted before surgery and it is possible that some viable tumour cells were missed on histological examination. One patient has survived over 4 years since tumour cells were found in her hysterectomy specimen suggesting that she required surgery. It is possible, however, that the tumour cells seen in the irradiated tissue were not necessarily viable (Suit & Gallagher 1964).

The fact that some patients with either very advanced or recurrent cervical carcinoma are now becoming long-term survivors suggests that the relatively high response rates we are seeing with chemotherapy may be of some long-term, as well as short-term, value. This high response rate should enable more patients to have radical surgery with curative intent. Further studies are therefore required for patients with stage I and II disease who have adverse prognostic factors, to determine the value of surgery immediately after chemotherapy, with radiotherapy then reserved for sites of residual disease.

Acknowledgments

We are grateful for the assistance of all the staff who helped manage these patients, our medical oncology colleagues, Professor K. D. Bagshawe and Dr R. H. J. Begent, who helped to design this study and for the close collaboration of our gynaeological colleagues Mr M. House, Mr M. Pawson and Mr C. Sims, and our radiotherapy colleagues E. Grosch, M. Glaser, S. Dische, M. Saunders and P. Strickland. We also thank our data manager D. Northcott.

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Received 24 November 1986
Accepted 2 February 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1212–1217

Primary adenocarcinoma of the cervix: treatment and results

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Summary. Between 1972 and 1983, 49 patients with adenocarcinoma of the cervix were treated in four ways: (i) radiotherapy alone, (ii) pre- or postoperative radiotherapy and a total abdominal hysterectomy and bilateral salpingo-oophorectomy, (iii) Wertheim's hysterectomy, and (iv) pre- or postoperative pelvic radiotherapy and Wertheim's hysterectomy. The 5-year survival results for patients with FIGO Stage I disease was 90%; with Stage II disease 60%; with Stage III disease 11% and none survived with Stage IV disease. All the patients, except one (Stage III), with well-differentiated tumours are alive and disease-free, irrespective of the type of treatment they received whereas only one patient out of the 13 who had poorly differentiated tumour is alive and disease-free. Three patients had bowel damage, one after radiotherapy alone and two after Wertheim's hysterectomy and postoperative radiotherapy. No major surgical complications occurred in this series.

There is increasing evidence that the prevalence of adenocarcinoma of the cervix has risen over the past two decades (Kyriakos *et al.* 1971; Tasker & Collins 1974; Davis & Moon 1975; Gallup & Abell 1977; Ireland *et al.* 1985). Some observers report an increase from 7·2% to as high as 15·1–18·5% of cervical carcinomas (Tamimi & Figge 1982; Shingleton *et al.* 1981).

The prognosis for adenocarcinoma has been reported in some series (Gallup & Abell 1977; Kjorstad 1977; Bergsjo 1963; Grundsell *et al.* 1979) to be less favourable than that for squamous cell carcinoma; while in others (Ireland *et al.* 1985; Abad *et al.* 1969; Kottmeier 1964; Marcus 1963), no significant difference has been found. There is considerable controversy about the most appropriate treatment of adenocarcinoma of the cervix; with early primary disease, there are proponents of the use of radiotherapy alone (Abad 1969; Kottmeier 1964; Cuccia *et al.* 1967; Weiner & Wizenberg 1975) and those who recommend a combination of irradiation and operation (Haggard *et al.* 1964; Kagan *et al.* 1973; Rutledge *et al.* 1975; Milsom & Friberg 1983). The aim of the present study was to assess the treatment, survival and complications in patients with adenocarcinoma of the cervix seen at St Thomas's Hospital, London, UK between 1972 and 1983. (Our unit is a referral centre for radiotherapy/surgery, from the South East Thames Region.)

Patients and methods

Fifty patients with adenocarcinoma of the endocervix were treated during the period of 12 years, 18% of all cervical carcinomas seen during this time. The age of these patients ranged between 31 and 80 (mean 57) years. The majority presented with postmenopausal bleeding (62%), and others with symptoms of postcoital bleeding (20%), intermenstrual bleeding

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(10%), menorrhagia (10%), and pelvic pain (4%). Eighteen patients (36%) were premenopausal. Only one patient was referred with an abnormal cervical smear found on routine screening. One patient with Stage I endocervical adenocarcinoma also had a primary breast carcinoma, she was treated with tamoxifen and had no treatment for her cervical carcinoma. Table 1 shows the FIGO stage of the remaining 49 patients who were studied. The patients have been followed from 4 to 132 months. No patient was lost to follow-up. The histological differentiation of the tumours in these patients was classified into well, moderately and poorly differentiated.

Treatment

The patients were divided into four groups according to the treatment they received: (i) radiotherapy alone, (ii) pre- or postoperative radiotherapy and a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH BSO), (iii) Wertheim's hysterectomy and (iv) pre- or postoperative pelvic radiotherapy and Wertheim's hysterectomy. Two patients with FIGO Stage IV disease underwent pelvic exenteration. The choice of more radical surgery (Wertheim's) depended on the stage and general condition of the patient. Age was not taken into consideration for the extent of surgery, although most of the patients who had a Wertheim's hysterectomy were premenopausal (age: range 31–75, mean 40 years).

Radiotherapy alone

Until 1978, patients with adenocarcinoma of the cervix, Stages I, II and III, were treated with two intracavitary insertions, 2 weeks apart, followed by a course of external cobalt-60 teletherapy to the pelvic lymph nodes. The intracavitary technique comprised an intrauterine and a central vaginal source in tandem, held in position by a vaginal applicator which could incorporate rectal shielding and allow afterloading of the vaginal component. Radium or other low dose-rate sources were used to deliver a total dose in the two insertions of approximately 55 Gy to point A and 15 Gy to point B. External radiotherapy with parallel opposed anterior and posterior fields plus a central rectangular shield was given in three fractions per week for 4 weeks (total 12 fractions) bringing the dose at point B up to 55 Gy.

Since 1978, the two radium insertions have been replaced by three insertions of high dose-rate cobalt-60 sources using an intrauterine tube and two lateral vaginal ovoids and a Cathetron afterloading machine, delivering a total dose to point A of 24 Gy. For Stage I and II disease, the insertions were carried out during the course of external radiotherapy (Table 2).

The external radiotherapy was given with an 8 MeV linear accelerator and the volume irradiated was individually simulated and planned for each patient. It included the nodes on the pelvic side walls and extended from the pelvic floor to the sacral promontory for patients with Stage I,

Table 1. Adenocarcinoma of the cervix: treatment and disease-free survival by FIGO stage

	Stage I		Stage II		Stage III		Stage IV	
Treatment	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Radiotherapy alone	3	0	3	5	1	5	0	5
TAH BSO + radiotherapy	2	0	5	0	0	2	0	0
Wertheim's hysterectomy	2	1	3	2	0	0	0	0
Wertheim's hysterectomy + radiotherapy	2	0	5	1	0	0	0	0
Abdominal pelvic resection	0	0	0	0	0	0	0	2
Total	9*	1	16	8	1	7	0	7

* Only 10 patients were treated with Stage I disease and nine of these are alive and free of disease.
TAH BSO = Total abdominal hysterectomy, bilateral salpingo-oophorectomy.

Table 2. Treatment schedule for high dose-rate intracavitary and external radiotherapy

Week	Monday	Tuesday	Wednesday	Thursday	Friday
1	ER (4)	—	ER (4)	—	ER (4)
2	IC	—	—	—	ER (2) + shield
3	ER (4)	—	ER (4)	—	ER (2) + shield
4	IC	—	—	—	ER (2) + shield
5	ER (4)	—	ER (4)	—	ER (2) + shield
6	IC	—	—	—	—

ER (4) and ER (2) = External radiotherapy, four-field and two-field technique.
IC = High dose-rate intracavitary insertion.

and to the lower border of L4 for those with Stage II and III disease. A dose of 41 Gy was delivered in 11 fractions over 33 days, all fields being treated on each occasion. For the first week the three fractions were treated with a four-field technique with no central shielding, and of the following eight fractions, four were given with two parallel opposed anterior and posterior fields with a central shield, and four with the four-field technique and no shield (Table 2).

Patients with Stage III disease had all the external radiotherapy first, using the four-field technique and no central shield, and received 41 Gy in 12 fractions over 28 days, followed by two insertions of 8 Gy, 2 and 4 weeks later. Patients with Stage IV disease were treated with palliative radiotherapy only.

Postoperative external radiotherapy

All patients who were treated with a total abdominal hysterectomy and bilateral salpingo-oophorectomy, and those who were found to have pelvic lymph node involvement at Wertheim's hysterectomy, received a radical course of external radiotherapy to the pelvis. No patient had postoperative vaginal vault irradiation. A four-field technique was used with the volume extending from the pelvic floor to the lower border of L4 and laterally to include the nodes on the pelvic side walls. Cobalt-60 teletherapy or an 8 MeV linear accelerator was used to deliver a dose of 42 Gy in 12 treatments over 4 weeks (three treatments per week).

Pre-operative intracavitary radiotherapy

Pre-operative radiotherapy was given in either of the following ways: two insertions a week apart using the radium technique described above, delivering a total dose of 60 Gy to point A, or two insertions 3 days apart using the high dose-rate cobalt-60 technique, delivering a total dose of 20 Gy to point A.

Results

For the 49 women the distribution of stage at presentation, the treatment schedule, and the number of patients alive and disease-free, is shown in Table 1. Life table survival curves (Kaplan & Meier 1958) were calculated for patients in the three FIGO stages respectively (Fig. 1).

Stage I

Only one patient with Stage I moderately differentiated tumour died. This was a 34-year-old woman who had had a Wertheim's hysterectomy and had no tumour in the lymph nodes at the initial surgery. However, she was found to have pelvic recurrence 30 months after the hysterectomy and died 2 months later. As shown in Table 3, all the patients with a well-differentiated tumour in Stage I are alive and disease-free, irrespective of the type of treatment they received.

Stage II

Amongst the eight patients who died following treatment for Stage II tumours, five had radiotherapy only and three had Wertheim's hysterectomy and radiotherapy; of these three, one patient died with peritonitis and bowel obstruction as a complication of treatment. Two patients developed recurrent pelvic tumour and para-aortic node tumour 3 and 4 years after initial treatment and died of the disease. All the five women who were treated with TAH BSO +

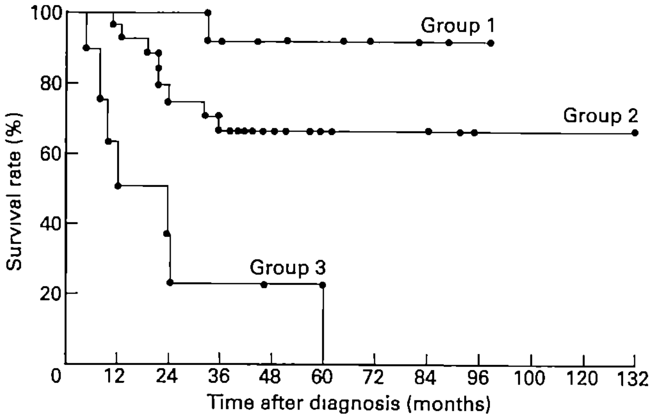

Fig. 1. Five-year survival of patients with Stages I, II and III adenocarcinoma of the cervix. Group 1 = 10 patients with Stage I disease, Group 2 = 24 patients with Stage II disease; Group 3 = 8 patients with Stage III disease.

radiotherapy for Stage II disease are alive and disease-free 3–7 years later.

Two patients with Stage II disease who had negative nodes at Wertheim's hysterectomy, but had moderately differentiated tumour, developed recurrent tumour. One of them had vaginal vault recurrence 4 months after, and the other had tumour in the pelvic wall 2 years after the hysterectomy. Both these patients responded to local radiotherapy and are disease-free 4 and 6 years later. All the five patients (Table 3) who had well-differentiated tumour are alive and disease-free irrespective of the type of treatment they received.

Stages III and IV

Only one patient with Stage III disease is alive and disease-free 3 years after radiotherapy. A second patient in this group lived without disease for 5 years after TAH BSO + postoperative radiotherapy but died of disseminated recurrence after 5 years. None of the patients with Stage IV responded to either radiotherapy or radical surgery. All the patients but one with advanced stage had moderate to poorly differentiated tumour (Table 3).

Complications

Three patients had bowel damage, one after treatment with radiotherapy alone, and two patients after Wertheim's hysterectomy and postoperative radiotherapy.

No major surgical complications occurred in this series.

Table 3. Relation between histological differentiation stage and survival in adenocarcinoma of the cervix

Histology	No of patients	Stage I		Stage II		Stage III		Stage IV	
		Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Well differentiated	11	5	0	5	0	0	1	0	0
Moderately differentiated	25	4	1	8 + 2*	2	1	2	0	5
Poorly differentiated	13	0	0	1	6	0	4	0	2
Total	49	9	1	16	8	1	7	0	7

* Two patients had recurrence following Wertheim's hysterectomy but are alive and disease-free after local radiotherapy.

Discussion

The incidence of adenocarcinoma in this study follows the upward trend observed by some of the recent reports (Ireland *et al.* 1985; Tamimi & Figge 1982; Shingleton *et al.* 1981), although this may be a relative increase due to an effective screening for cervical premalignancy preventing the development of invasive squamous cell carcinoma. In the present series, only one patient had abnormal cervical cytology before referral to a gynaecological unit. The failure to detect endocervical carcinoma on routine cervical smear may be because the conventional Ayre's spatula does not reach the endocervical canal. The increased frequency of invasive adenocarcinoma of the endocervix, however, poses the problem to the clinician of optimum method of treatment of patients with adenocarcinoma of the endocervix.

Although the number of patients in this study is small, analysis of tumour recurrence and patient survival suggests that surgery and radiotherapy are both effective forms of treatment. As regards the extent of surgery, our study does not show any advantage with Wertheim's hysterectomy over a simple TAH BSO + radiotherapy to the pelvis. On the contrary, patients treated with Wertheim's hysterectomy developed pelvic recurrence despite negative nodes. Ireland *et al.* (1985) treated 50 patients with Wertheim-Meig's radical hysterectomy but did not report the rate of recurrence associated with Stage I adenocarcinoma of the cervix. The disease-free survival in Stage I in our series (90%) is comparable to the 84% reported by Rutledge *et al.* (1975) and 90% reported by Shingleton *et al.* (1981) who used a combination of surgery and radiotherapy or radiotherapy alone.

Patients with Stage II adenocarcinoma do not appear to derive any advantage from radical Wertheim's hysterectomy in this or other series (Korhonen 1984 (38%); Ireland *et al.* 1985 (40%)). Rutledge *et al.* (1975), using a combination of simple hysterectomy and pre-operative radiotherapy in Stage II adenocarcinoma, reported a 53·7% 5-year survival compared with 41·9% in those treated with radiotherapy alone. They observed little improvement in survival by the addition of hysterectomy in patients with Stage I disease but a beneficial difference was seen in those with Stage II disease. This could perhaps be explained by the fact that Stage II disease tends to be bulky in volume and less well differentiated than Stage I, and a hysterectomy enables the removal of the gross tumour. Unlike Rutledge *et al.* (1975) and Shingleton *et al.* (1981), we prefer postoperative rather than preoperative radiotherapy in our unit as we believe this allows better assessment of histological differentiation and extent of the tumour in the operative specimen than an irradiated uterus.

Like other workers, we observed poor results in patients with Stage III and IV disease. This group of patients in future may benefit by adjuvant chemotherapy in addition to radiotherapy and surgery.

Acknowledgment

Our thanks to Richard Morris (Lecturer in Medical Statistics) and Khalid Khan (Statistical Assistant), Department of Community Medicine, St Thomas's Hospital, for their statistical help.

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Received 19 January 1987
Accepted 6 April 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp 1218–1222

Progesterone inhibition in mid-trimester termination of pregnancy: physiological and clinical effects

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Summary. A double-blind, placebo controlled clinical trial was conducted to assess the clinical and physiological effects of 'epostane', a progesterone synthesis inhibitor, in mid-trimester prostaglandin termination of pregnancy. Mean peripheral progesterone levels had fallen by 74% after 72 h in the patients treated wtih epostane. The mean induction–abortion interval in the treatment group was 490 (SD 271) min, compared with 1432 (SD 640) min in the control group. Intrauterine pressure recording demonstrated increased sensitivity to prostaglandin E_2 after epostane treatment but no change in oxytocin sensitivity. The clinical implications of facilitated induction of abortion are discussed.

Epostane (4,5 epoxy-17 hydroxy-4,17 dimethyl 3 oxo androstane-2 carbonitrile, WIN 32729, Sterling Winthrop, Guildford, Surrey) is a synthetic steroid which has been shown to inhibit in-vivo steroid synthesis by competitive inhibition of the 3-beta hydroxysteroid dehydrogenase delta 4–5 isomerase enzyme system resulting in decreased production of progesterone and an increase in its biologically inactive precursor pregnenolone (van der Spuy *et al.* 1983). This results in a reduction in peripheral serum progesterone levels in both the first and second trimesters of human pregnancy indicating inhibition of both luteal and placental/decidual synthesis (Pattison *et al* 1985*a,b*). Since progesterone is believed to inhibit myometrial contractility during pregnancy (Csapo *et al.* 1973), the clinical and physiological effects of exogenous oxytocics following suppression of this inhibition have been examined in patients undergoing therapeutic termination of pregnancy during the second trimester.

Subjects and methods

The double-blind, placebo controlled trial included 10 healthy primigravidae at 13–18 weeks gestation who were scheduled to have a prostaglandin induced abortion within the terms of the 1967 Abortion Act. The study was small because epostane, a new pharmaceutical agent, was being used as an adjunct to treatment in a relatively uncommon clinical situation. Gestational age was calculated from menstrual dates and confirmed with ultrasonography. After giving informed consent to the study, each patient was given a bottle, numbered 1–10, labelled 'Epostane 100 mg, 1 tablet to be taken on waking, 1 tablet to be taken at 2.00 p.m. and 1 to be taken on going to bed'; each bottle contained nine tablets of either epostane 100 mg or a physically identical placebo. The last tablet was to be taken on the morning of admission to hospital. The bottles were prepared by Sterling Winthrop, Research Development (SWRD), Alnwick, Northumberland, and sealed copies of the code identifying the contents of each bottle were held by SWRD Guildford and Alnwick. Randomization was performed by SWRD using

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predetermined randomization schedule balanced within the group of 10.

Before the patients started taking the tablets, a peripheral venous blood sample was obtained for haematological (Hb, WCC, platelets, group), biochemical (Na+, K+, Cl−, HCO3−, urea, creatinine, albumin, AST, gamma-glutamyl TP, alkaline phosphatase) and hormonal (progesterone, oestradiol, aldosterone, cortisol and prostaglandins) analyses, (pretreatment). The blood tests were repeated on admission to hospital 3–5 h after the last tablet had been taken (post-treatment), and after abortion (post-abortion), but before surgical evacuation of the uterus when this was necessary.

Before and after taking the tablets patients were asked specific questions about uterine pain, vaginal bleeding, threatened or spontaneous abortion and any symptoms that could have been due to side-effects or drug reactions. The answers were recorded on each treatment protocol by one author (M.S).

On admission to hospital each patient received an intravenous infusion of N/5 dextrose saline and a Gaeltec pressure tip catheter was introduced transcervically into the extra-amniotic space and retained by ligature to a 14 G Foley catheter with a 5 ml balloon. Uterine pressure was recorded directly onto magnetic discs and 10-min epochs were later analysed using a program quantifying uterine activity in uterine activity units (UAU) (Hon & Paul 1973). Analysis of variance was used to assess the effect of the treatment on uterine activity.

After a 30-min recording of 'baseline' intra-uterine pressure, a metered intravenous infusion of oxytocin (Syntocinon, Sandoz) was started at a rate of 2 mu/min and this was increased exponentially at 10-min intervals to a maximum of 64 mu/min. Intrauterine pressure recording was continued throughout (60 min). The intravenous infusion of oxytocin was then stopped. Prostaglandin E_2 (PGE_2) (Upjohn) 1·5 mg in 10 g of 6% Tylose gel was introduced into the extra-amniotic space through the Foley catheter and uterine activity was recorded for a further 60 min before the removal of the catheters. Six hours after the PGE_2 injection, a constant infusion of oxytocin 100 mu/min in N/5 dextrose saline was started and maintained until abortion. Vital signs, side-effects and blood loss were recorded at 2-h intervals. Papaveretum 20 mg and chlorpromazine 25 mg were given intramuscularly for pain relief when required. If clinical examination suggested incomplete abortion, the uterus was evacuated surgically.

Clinical progress, side-effects, symptoms, blood pressure, temperature and pulse rate were also recorded at clinically appropriate time intervals on the World Health Organization 'Task Force' mid-trimester termination of pregnancy record sheets. All patients were managed by two of the authors (M.S., J.F.).

Results

Table 1 gives patient details for the treatment and control groups. There were no statistically significant differences between the two groups (Mann–Whitney *U*-test).

Uterine pain, vaginal bleeding or spontaneous abortion did not occur in any patient before admission to hospital. No drug reactions or side-effects were recorded during the treatment period before admission to hospital.

The induction–abortion interval was the time in minutes between the extra-amniotic injection of PGE_2 gel and abortion of the fetus. Patients given epostane (the treatment group) had a mean induction–abortion interval of 490 (SD 271) min compared with 1432 (SD 640) min in the control group ($P<0{\cdot}05$, Mann–Whitney *U*-test). One patient in the control group aborted after 42 h 20 min; all the patients in the treatment group had aborted within 16 h. There was no obvious difference in side-effects (symptoms and signs) or blood loss (clinical estimate) between the two groups as assessed by retrospective examination of the WHO record sheets. Each patient in the treatment group required one injection for analgesia, whereas all five patients in the control group required more than one injection (four required two and one required three injections) ($P<0{\cdot}01$, Fisher exact test).

Figure 1 illustrates the mean uterine activity

Table 1. Characteristics of patients in the epostane and control groups

	Control ($n = 5$)	Study ($n = 5$)
Age (years)	18·0 (1·8)	21·9 (3·2)
Height (cm)	161·2 (3·0)	154·8 (3·1)
Weight (kg)	57 1 (11·2)	57·1 (9·0)
Gestation (weeks)	16·6 (1·3)	16 4 (2 8)

Results are means (SD)

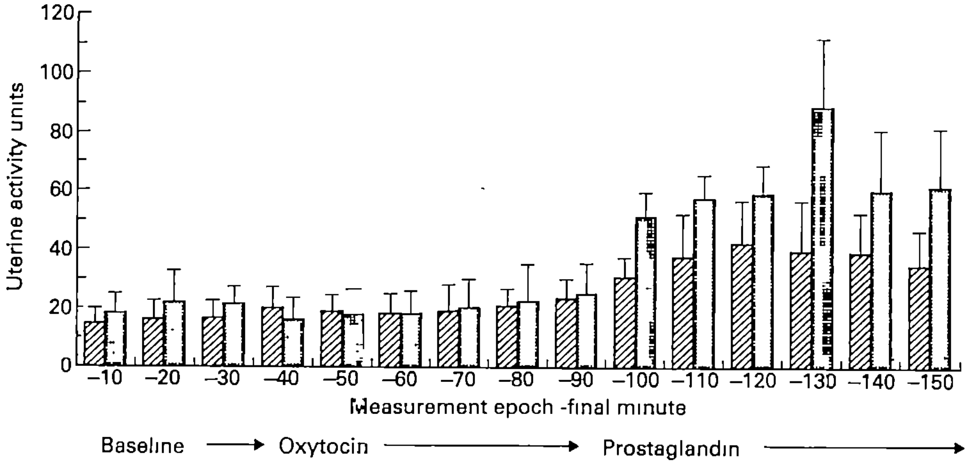

Fig. 1. Uterine activity measured in uterine activity units (mean + SE), in the epostane ($n = 5$) (■) and control ($n = 5$) (▨) groups for each 10-min epoch during the baseline, oxytocin and prostaglandin phases of the study

measured in UAU during the three phases of the study: (i) baseline, recorded before any stimulation, (ii) during oxytocin, and (iii) during prostaglandin stimulation in the epostane and control groups.

Three-way analysis of variance (times (10-min epochs), treatments, patients within treatments) was used to assess differences between the epostane and control groups for each phase of uterine activity measurement separately (baseline, oxytocin and prostaglandin).

Baseline phase. There was a statistically significant difference in uterine activity between the epostane and control groups in the baseline phase with the epostane group having the greater mean ($P<0{\cdot}005$, $F = 14{\cdot}87$). There was no significant difference between the times but there were significant differences between the individual patients ($P<0{\cdot}0005$, $F = 10{\cdot}32$).

Oxytocin phase. There was no significant difference in uterine activity between the epostane and control groups but there were significant differences between the times ($P<0{\cdot}001$, $F = 5{\cdot}39$) and between individual patients ($P<0{\cdot}001$, $F = 35{\cdot}68$).

Prostaglandin phase. There was some evidence to suggest that there were differences between the times; however, this was not significant at the 5% level. There was a statistically significant difference between the epostane and control groups with the epostane group showing greater uterine activity ($P<0{\cdot}001$, $F = 33{\cdot}34$) and there were significant differences between individual patients ($P<0{\cdot}001$, $F = 4{\cdot}07$)

Table 2 shows the maternal, peripheral, venous, serum steroid levels at the three sampling times in the two groups.

In the post-treatment samples mean progesterone levels were significantly lower in the epostane group than in the control group ($P<0{\cdot}05$, Wilcoxon two-sample test). Within

Table 2. Peripheral maternal venous serum steroid levels at three sampling times in the two groups

Steroid	Group	Sampling time Pretreatment	 Post-treatment	 Post-abortion
Progesterone	Epostane	30 (11)	8 (4)	4 (2)
(ng/ml)	Control	27 (6)	32 (9)	7 (2)
Oestradiol	Epostane	1·4 (0·8)	0·9 (1·1)	0·6 (0·8)
(nM/l)	Control	1·2 (0·8)	1·5 (0·9)	0·3 (0·1)
Cortisol	Epostane	251 (123)	255 (47)	305 (109)
(nM/l)	Control	234 (100)	240 (82)	440 (245)

Results are means (SD) values, there were five subjects in each of two groups group analysis showed significant decreases for the epostane group from the pretreatment progesterone levels in the post-treatment and post-abortion samples ($P<0{\cdot}01$ and $P<0{\cdot}005$ respectively, paired *t*-test) and a significant decrease in the post-abortion sample for the control group ($P<0{\cdot}005$, paired *t*-test) compared with the pretreatment value.

There were no statistically significant differences in oestradiol levels between the epostane and control groups at any of the sampling times. Within the epostane group the oestradiol level was significantly lower in the post-abortion sample than in the pretreatment sample ($P<0{\cdot}05$, paired *t*-test).

There were no statistically significant differences in cortisol levels at the three sampling times between or within the two groups. The time of day at which the samples were taken for pretreatment and post-treatment cortisol levels measurement were not significantly different (Wilcoxon two-sample test).

There were no statistically significant differences between the treatment and control groups in any of the haematological, biochemical or hepatic enzyme indices measured at any of the sampling times.

Discussion

The rationale for the use of epostane as an adjunct to prostaglandin induction of abortion depends on its ability to inhibit placental/decidual progesterone synthesis which we reasoned would sensitize the myometrium to endogenous/exogenous oxytocics by removing the progesterone 'block' described by Csapo (1973). Lopez-Bernal *et al.* (1986) demonstrated that epostane inhibits progesterone production in human chorio-decidua *in vitro* and Huszar (1980) has described the probable intracellular site of the progesterone 'block'. Our clinical data are in agreement with their respective biochemical and theoretical evidence.

Our results confirm that epostane significantly reduces peripheral progesterone levels during the second trimester of pregnancy. After 72 h of treatment with epostane the mean progesterone level (8 ng/ml) was 74% lower than the mean level before treatment (30 ng/ml). Peripheral oestradiol and cortisol levels were not significantly different after treatment, supporting the theory that epostane inhibits placental/decidual progesterone synthesis without significantly affecting adrenal steroidogenesis

In this hospital the preferred technique for induction of second trimester abortion between 13 and 17 weeks gestation is extra-amniotic injection of PGE_2 folllowed 6 h later by an intravenous oxytocin infusion. MacKenzie & Embrey (1976), using an identical regime with 1.5 mg PGE_2, reported a mean induction–abortion interval of 978 (SD 66) min in a group of women of mixed parity between 9 and 24 weeks gestation. The difference in gestational age and parity between their group and our patients could explain the significantly higher mean induction–abortion interval of 1432 (SD 640) min recorded in our control group. However, in our study the epostane group had a mean induction–abortion interval of 490 (SD 271) min which was significantly lower than that in our control group or that reported by MacKenzie & Embrey (1976) for their mixed group These results confirm the efficacy of epostane in shortening the induction–abortion interval in mid-trimester prostaglandin-induced abortions.

The reduction in the induction–abortion interval was of considerable benefit to the patients in that parenteral narcotic analgesia and the duration of intravenous oxytocin were both reduced, together with the potential of reduced in-patient stay, all factors which contribute to the procedure-related morbidity. In addition, PGE_2 has dose-related gastrointestinal side-effects (MacKenzie & Embrey 1976), which could be minimized by using the smallest possible 'effective' dose of prostaglandin after epostane 'priming'. Day-case prostaglandin termination of mid-trimester pregnancy becomes a realistic possibility after anti-progesterone priming. Furthermore by modifying the dose, timing or duration of the priming or by using a different dose or form of prostaglandin, medical induction of mid-trimester abortion may become possible.

The quantification of myometrial sensitivity with intrauterine pressure measurements confirmed that there was increased baseline myometrial activity (endogenous oxytocic effect) after treatment with epostane and after PGE_2 injection (exogenous effect); however, no change in sensitivity to oxytocin was demonstrated. This may be because the dose used was too small or the duration of the infusion too short. In addition it is unlikely that the myometrium would have developed active oxytocin receptors at this stage of pregnancy or that a 60-min oxytocin infusion is a large enough stimulus to receptor formation.

These data support the hypothesis that the gravid uterus is an organ suppressed by progesterone which becomes more active after its withdrawal and leads to a marked increase in its sensitivity to exogenous oxytocics. While elucidation of the exact endocrine mechanism which initiates 'normal labour' remains difficult, progesterone inhibition has been demonstrated as an effective 'priming' procedure which could be immediately realized in the treatment of mid-trimester termination of pregnancy, missed abortion and intrauterine fetal death.

Acknowledgments

This work was supported by Sterling Winthrop Research & Development, Guildford, Surrey, and had the approval of the Oxford Region Ethical Committee.

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Received 10 December 1986
Accepted 10 March 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1223–1224

A multiple pregnancy after in-vitro fertilization. Case report

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Case report

This 32-year-old, twice married, patient had her first pregnancy in 1983; it was a left tubal ectopic which was treated by salpingectomy. In 1984, laparoscopic examination showed a right hydrosalpinx and left sided periovarian adhesions. A right cuff salpingostomy and lysis of adhesions around the left ovary were then performed.

She failed to become pregnant and in August 1985 she was referred to the Cromwell Hospital, London, for consideration of in-vitro fertilization (IVF) and embryo replacement. In September, preliminary laparoscopy showed that both ovaries were accessible for oocyte recovery and that only a slight trickle issued from the right tube after dye injection.

On a day-care basis, ovulation was stimulated with clomiphene, 100 mg on days 2–6, and pergonal, four ampoules injected intramuscularly on days 5–11. On 20 November she had a laparoscopic aspiration of four oocytes which were fertilized with her husband's freshly washed semen. The four embryos which resulted were introduced into her uterus 48 h later. Four weeks later a biochemical pregnancy was diagnosed by beta-hCG estimation. On 15 January, 1986, a clinical pregnancy was confirmed at the Northern antenatal clinic; she was well with a blood pressure of 110/70 mmHg, she weighed 61·5 kg, urine examination was normal, her blood group was A rhesus positive, VDRL was negative and she was rubella immune.

An ultrasound scan showed three sacs, each containing a fetus equivalent to 11 weeks gestation, this was confirmed by a second scan on 10 March.

Ten days later at 19 weeks gestation she was admitted as an emergency with a prolapsed cord of the first fetus and a cervical dilatation of 3 cm. There were no fetal heart sounds from the first fetus but sounds were present from the other two fetuses. A high vaginal swab was obtained, she was prescribed antibiotics and given an intravenous infusion of ritodrine. Four hours later she was examined under anaesthesia in the operating theatre. The cervix was now 4 cm dilated and a fetal arm had prolapsed into the vagina. A fetal leg was identified and the leading fetus was extracted by the breech. The fetus was male, macerated, and weighed 240 g. The cord was excised close to the placental disc which was left inside the uterus. A mersilene tape cervical suture was inserted to close the cervical canal.

Tocolytic therapy and fetal cardiotocography were maintained for the next 48 h and then discontinued. The patient was afebrile and she remained in the antenatal ward. The twin pregnancy continued normally and two further scans at 21 and 25 weeks confirmed the satisfactory growth of both babies.

At 28 weeks gestation, uterine contractions were detected and pelvic examination showed a bulging bag of membranes presenting through the cervix which was 5 cm dilated.

The cervical suture was divided and removed under epidural analgesia and the membranes were left intact. The membranes ruptured 4 h later and clear amniotic fluid was released. As the presenting fetus was cephalic, labour was allowed to continue. Six hours after the onset of labour, fetal cardiotocography showed Type I dips, and a vaginal examination detected a face presentation with a loop of cord lying behind and above the head. Pressure was kept off the cord by a hand in the vagina with the patient in the left lateral position, and 20 min later she was delivered by lower segment caesarean section

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under general anaesthesia. The first baby was a boy weighing 1350 g and the second was a girl weighing 1120 g. Three separate placentas were removed from the uterus (total weight 1725 g), one of which was dehydrated.

Both babies required intubation and ventilation and were given prophylactic antibiotics. They were extubated within 48 h and subsequently made good progress in the special care nursery.

The mother recovered well and was discharged home on 3 June and the babies were discharged 6 weeks later.

Comment

Since 1979, when P. C. Steptoe and R G. Edwards (unpublished lecture) announced the possibility of in-vitro fertilization and embryo replacement, well over 1000 babies have been born after IVF. Most of the patients selected have tubal disease, like our patient, although the indications have expanded to include the male factor, endometriosis and unexplained infertility

With improved knowledge the 'take home baby' rate has risen to about 30% in selected cases, but substantial pregnancy losses still occur. To reduce the failure rate, some centres have a policy of replacing several embryos, thus leading to an increased risk of multiple pregnancy (Kerin *et al.* 1983). Steptoe (1985) proposed that not more than three embryos should be replaced, but other workers have introduced as many as six after suitable counselling of the parents (Australian In-Vitro Fertilisation Collaborative Group 1985). Multiple pregnancies are associated with a substantially greater perinatal mortality rate than singleton pregnancies, due largely to premature delivery (Andrews *et al* 1986). IVF pregnancies are associated with a higher than normal premature birth rate and multiple pregnancies are a contributory factor. As the number of babies increases so individual birthweights decrease and over 80% of triplets weigh <2500 g. Furthermore, multiple births alter the lifestyle of parents and may produce psycho-social problems with often unacceptable physical, emotional and financial stress.

Our patient experienced some of these problems. The triplet pregnancy could not be sustained and the leading fetus died, presumably following cord prolapse. Three separate scans confirmed that the remaining two fetuses continued to grow and fortunately labour was averted by the sympathomimetic drug infusion, after the dead fetus was removed and the cervical suture inserted. Spontaneous premature labour occurred at 29 weeks with the complication of malpresentation and prolapse of the cord. The two infants survived thanks to the prompt caesarean section and expert paediatric supervision.

It has been suggested that in all triplet and quadruplet pregnancies cervical cerclage should be undertaken at about 12 weeks (I. Craft 1986, personal communication) or that oral sympathomimetic drugs should be given to postpone the onset of premature labour until survival of the fetuses is likely. Our experience supports this view and also confirms the view that not more than three embryos should be replaced after IVF.

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Received 27 March 1987
Accepted 27 July 1987

British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp. 1225–1228

CORRESPONDENCE

Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level

Dear Sir,

The article by Cuckle *et al.* [*Br J Obstet Gynaecol* (1987) **94**, 387–402] filled me with dismay In our health district, which enjoys a rather low incidence of neural tube defect, we have never offered the serum alpha-fetoprotein (AFP) test as a screen. Those few that we do seem to cause inordinate disruption to the smooth running of the clinics and very considerable patient anxiety is created whenever a false positive crops up. We have preferred instead to opt for high quality ultrasound screening at 16–18 weeks gestation which never arouses anxiety as all patients expect to have an ultrasound scan done.

It seems that we are not alone in this opinion and a recent survey of the 17 health districts in the Yorkshire Regional Health Authority discloses that only six districts aim to screen all their pregnant women antenatally.

Are we now to understand that the AFP test, which has always been unsatisfactory for many obstetricians, should now be resurrected to try and predict the risk of Down's syndrome more efficiently?

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Dear Sir,

I read with interest the six Down's syndrome screening policies proposed by Cuckle *et al.* [*Br J Obstet Gynaecol* (1987) **94**, 387–402], having just completed a 5-year retrospective study on the value of AFP screening for neural tube defects and Down's syndrome pregnancies in our hospital (paper in preparation) and concluding that it is not a useful diagnostic tool

During the screening period there were 15 352 unaffected pregnancies and 18 pregnancies affected by Down's syndrome from which 12 AFP results were available for further analysis. When the results were compared with the two screening policies proposed by Cuckle *et al.* (1984) no more Down's pregnancies would have been picked up than by screening based solely on advanced maternal age.

The recent publication prompted us to make further calculations from the 12 AFP results to assess the pick-up rate when screening patients with a risk of >1 in 350, according to the published tables using maternal age, maternal serum AFP and gestational age based on both fetal biparietal diameter (BPD) and menstrual age (LMP). On this occasion, one case of Down's syndrome would have been detected if amniocentesis had been offered based on the gestational age according to the LMP for a risk of 1 in 260 (the risk based on the gestational age according to BPD was 1 in 430 as there was a 2-week discrepancy between the ultrasound and the menstrual dates). It is interesting to note that previously Cuckle & Wald (1987) concluded that the effect of estimating gestational age by ultrasound to interpret AFP results would not have much effect on the sensitivity of AFP screening for Down's syndrome; in this case it would have been reduced, because in this hospital the BPD is used to interpret AFP results.

I appreciate that the numbers in this study are small, but if screening had been introduced in this hospital 5 years ago, it would have led to a number of women undergoing unnecessary amniocentesis with no positive results I could suggest that AFP screening is not effective for our population because the average age is less than that in other studies (50% under 25 years) resulting in a lower incidence of Down's syndrome (1 in 808). However, I must concur with Spencer & Carpenter (1985) that caution is needed before the widespread introduction of this method of screening for Down's syndrome pregnancies in all populations.

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Authors' reply

Dear Sir,

Mr Neale's preference for ultrasound over maternal serum alpha-fetoprotein (AFP) measurement as a method of screening for neural tube defects is a statement of faith. Unfortunately, there are insufficient data available to judge whether this view is sound. In the study reported from Malmo, Sweden by Persson *et al.* (1983) where pregnant women were screened by ultrasound and had a serum AFP test at their first antenatal visit, there were eight who had pregnancies associated with spina bifida. Six had positive serum AFP results and two did not; two affected pregnancies were identified by ultrasound and six were not. In the study reported from London by Campbell & Smith (1984), routine ultrasound detected eight out of eight spina bifida pregnancies (no serum AFP results were reported). The ultrasound detection rate for both studies combined was therefore 62% (10/16). There were no ultrasound false-positives in the Swedish study and data on false-positives were not published in the King's study report. The results are summarized in Table 1.

A related question is whether or not an ultrasound examination should replace amniocentesis as the diagnostic procedure in women who are at high risk of a neural tube defect pregnancy usually on account of a positive maternal serum AFP test or because of a family history of neural

Table 1. Ultrasound detection of neural tube defects: detection and false-positive rates*

Study	Detection rate (%)†				False-positive rate (%)‡	
	Anencephaly		Spina bifida			
Routine ultrasound						
Persson *et al.* (1983)	100	(1/1)	25	(2/8)	0·0	(0/10 137)
Campbell & Smith (1984)	100	(5/5)	100	(8/8)	NK	(NK/11 651)
Combined	100	(6/6)	62	(10/16)	0 0	(0/10 137)
Selective ultrasound						
Robinson *et al.* (1980)	100	(39/39)	79	(15/19)	0·0	(0/302)
Hobbins *et al.* (1982)	—	—	100	(6/6)	0·0	(0/22)
Roberts *et al.* (1983)						
Study 1	100	(31/31)	33	(6/18)	3·9	(49/1243)
Study 2	100	(26/26)	80	(16/20)	0·3	(4/1171)
Campbell *et al.* (1984)	100	(48/48)	94	(112/119)	0·2	(3/1306)
Gough (1984)	100	(23/23)	100	(19/19)	3·0	(6/201)
Sabbagha *et al.* (1985)	100	(5/5)	75	(6/8)	2·2	(2/92)
Combined	100	(172/172)	86	(180/209)	1·5	(64/4337)

* Spina bifida includes encephalocele, routine ultrasound performed on all women regardless of NTD risk, selective ultrasound on women at high risk of NTD.

† Proportion of affected pregnancies with ultrasound suspicion of NTD (number of affected pregnancies in parentheses).

‡ Proportion of unaffected pregnancies with ultrasound suspicion of NTD (number of unaffected pregnancies in parentheses)

NK, not known.

tube defect. To do so the performance of ultrasound would need to be at least as good as that achieved by amniotic fluid AFP and acetylcholinesterase measurement. Table 1 summarizes the results from six studies in which ultrasound was used to diagnose neural tube defects in high-risk pregnancies. The detection rate for spina bifida for the six studies combined was 86% (180/209) and the false-positive rate 1·5% (64/4337)—a diagnostic accuracy much less than that for amniotic fluid AFP and acetylcholinesterase measurement (UK Collaborative AFP Study 1979; Collaborative Acetylcholinesterase Study 1981).

If the diagnostic accuracy of alternative when used in high-risk pregnancies can be achieved in the general population and at an acceptable cost, then there would be a case for ultrasound replacing AFP screening for neural tube defects. Until this has been demonstrated, there is no basis for abandoning AFP screening, with its known performance, in favour of an alternative unevaluated approach. The Medical Research Council has recently agreed to support a multicentre study aimed at estimating the diagnostic efficiency of ultrasound both in high-risk pregnancies and in the general population.

Dr Bisson concludes that AFP screening is not useful for the detection of Down's syndrome since, among 12 affected pregnancies studied, no more would have been detected by combined AFP and age screening than were detected by maternal age alone. This is too small a series on which to base such a conclusion. There is now no doubt that maternal serum AFP levels are, on average, reduced in Down's syndrome pregnancies; the weighted geometric mean value from all 13 published series including a total of 405 cases is 0·76 multiples of the normal median (Wald & Cuckle 1987). The reduction in maternal serum AFP is present in younger women as well as in those of advanced maternal age (Cuckle *et al.* 1984). It follows that the combination of serum AFP and maternal age will result in a higher detection rate for Down's syndrome, for a given proportion of women having an amniocentesis, than can be achieved by using age alone.

The practical benefits of combined AFP and maternal age screening for Down's syndrome have been demonstrated by the New England Regional Genetics Group (Palomaki 1986). Using a Down's syndrome risk cut-off level of 1:270 at the mid-trimester of pregnancy (the risk of a 35-year-old woman as judged by the study group) an extra 10 Down's syndrome pregnancies were detected out of the 51 141 women aged under 35 years who were screened. This represents an increase in the Down's syndrome detection rate in the whole population by at least one third, a notable benefit.

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The effect of severe pre-eclampsia on the pancreas: changes in the serum cationic trypsinogen and pancreatic amylase

Dear Sir,

Haukland *et al.* [*Br J Obstet Gynaecol* (1987) **94**, 765–767] report the effects of pre-eclampsia on the pancreas. I have long considered pancreatitis as a manifestation in some patients with pre-eclampsia (gestosis) and routinely order serum and urine amylase studies in these patients. Pregnant patients with elevated amylase sometimes respond dramatically to treatment of their 'pancreatitis' (Goodlin 1983, 1986).

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British Journal of Obstetrics and Gynaecology
December 1987, Vol. 94, pp 1229–1232

BOOK REVIEWS

A Neonatal Vade-Mecum edited by Peter J. Fleming, Brian D. Speidel & Peter M. Dunn. Lloyd-Luke (Medical Books) Ltd, London, 1986, 334 pages with figures and tables, £13.50

As neonatal intensive care units sprang up like mushrooms throughout the country, each produced its own working loose-leaf folder telling the new residents how things were done. Such information was not obtainable from standard textbooks and anyway was frequently parochial in nature. Subsequently many of these folders of notes have metamorphosed into 'handbooks of neonatal intensive care' and at first I thought that *A Neonatal Vade-Mecum* was just another one of these. However, this small volume, conveniently sized for the standard NHS white coat pocket, is a lot more than this. It manages to cram an enormous amount of readily available information into just over 300 pages. It also manages to be much more than just a guide to neonatal intensive care, covering all aspects of special care and of care for the baby warded in with its mother. In such a book it is very easy to be critical of minor details of practice which vary from centre to centre but with the occasional exception, the Bristol team seem to have avoided most of these. They have also managed to avoid long dreary lists of what should be on particular equipment trolleys which are commonly seen in such books. It is up-to-date, with information on what to do with babies born to HIV positive mothers, a section on cranial ultrasound and another on the problems of drug abuse by mothers, as well as the expected sections on examining the newborn and the management of respiratory disease in the intensive care unit. There is a good section on practical procedures and a detailed therapeutic appendix, although the presbyopic will require glasses to use it. An excellent chapter on the care of the family is followed by a very useful appendix containing the names and addresses of dozens of self help organizations for infants and their families

The book even has room for a short but sensible chapter on medical ethical problems in malformed or potentially handicapped infants. I have given the book a 'test drive' with our recent intake of residents, and they are very enthusiastic about it. At the price this little book is very good value not only to neonatologists in training but to midwives and obstetricians as a daily source of reference.

Richard Cooke

Chorion Villus Sampling edited by D. T. Y. Liu, E. M. Symonds & M. S Golbus. Chapman & Hall, London, 1987, 362 pages with figures and tables, £27.50

This modestly sized and (by today's standards) reasonably priced book offers a timely compilation of both the clinical and laboratory techniques necessary to achieve a successful sample of chorionic villi.

There are five major sections which deal with the structure and function of the trophoblast, different techniques for acquiring the sample, the clinical applications, methods of chromosome and DNA analysis, and a final section discussing genetic counselling. The section dealing with the various methods used for obtaining a sample of chorion details so many ways that it must be assumed that the 'ideal' technique has yet to be decided upon.

The chapters concerned with chromosome analysis and DNA techniques are commendably brief while being informative and interesting. They recommend themselves particularly to those training to be obstetricians who wish to improve their understanding of, for example, the counselling difficulties caused by mosaicism and aneuploidy.

If there is a weakness to the structure of this book it is the inclusion of a section dealing with the prenatal diagnosis of fetal conditions during the second trimester using ultrasound techniques; methods for possibly correcting some fetal malformations are also discussed. While interesting and comprehensive, such discussions are hardly relevant to the subject in hand

The publishers deserve criticism for one feature: there are too many virtually blank pages between sections. About 16 pages add nothing to the presentation and one is left with the feeling they are acting as a 'fill' to make the book look bigger(?) This feature aside, the book covers its chosen topic well and the diagrams and photographs are clear. The editors are to be commended for achieving a relatively uniform style for what is actually a multi-author work.

Elizabeth A. Ryall

Human Embryo Research: Yes or No? edited by The Ciba Foundation. Tavistock Publications, London, New York, 1986, 223 pages with figures and tables, £6.95

This book contains contributions from members of a study group convened at the Ciba Foundation in November 1985, each being followed by a report of the discussion it engendered. They covered not only the scientific but also the legal, religious, sociological, ethical and moral dimensions of the problem. The fields in which research on human embryos might be useful (mechanism of infertility, in-vitro fertilization, diagnosis of hereditary disease, causes and avoidance of congenital malformations, improvement of contraception) are examined in detail.

No one would dispute that research on human embryos is potentially useful. However, a very important free-standing discussion on the 'status of the pre-embryo' (i.e. the pre-implantation embryo) highlights the crucial issue of whether any precise stage or time period in the development of the embryo after fertilization can be defined as the starting point of life, after which the embryo should be entitled to the protection and respect normally awarded to a living human being but before which such protection and respect may be waived. There can be no absolute and unequivocal answer to such a question and research on embryos should, ideally, not be guided by the principle of utility and the setting of an arbitrary point, such as 14 days after fertilization, for the beginning of life. There is no authority, temporal or spiritual, for such a pronouncement.

It should be remembered that the recommendation made by the Warnock Committee on Human Fertilization and Embryology in July 1984 to establish such a specific point at 14 days after fertilization, before which research on human embryos would be permissible, was by no means unanimous. Thus, of the 16 members of the committee, three dissented totally in that they wished to ban such experimentation altogether and to allow embryos to be handled only with a view to implantation, while four dissented partially in disagreeing with the use of embryos in research if they were created for that purpose rather than for implantation, or if they came into existence as a result of other research.

Attempts to bring in legislation which would ban embryo research altogether, such as The Unborn Children (Protection) Bill, introduced by Mr Enoch Powell in February 1985, have been unsuccessful. Any future attempt at legislation should be based on a moral consensus within society, and books such as this represent important milestones on the difficult road towards reaching such a consensus. While awaiting this definition and the corresponding legislation, the Medical Research Council and the Royal College of Obstetricians and Gynaecologists have set up a voluntary licensing authority to examine proposals in this field.

G. R. Fraser

Diagnostic Picture Tests in Obstetrics and Gynaecology by H. Joyce, J F. Patrick, G. D. Reid, F. L Wilcox & V. R. Tindall. Wolfe Medical Publications Ltd, London, 1987, 219 pages fully illustrated, £6.50

Clinical photographs are not for the squeamish. No matter how sharp the focus or how lush the colour, a picture of a diseased organ is somehow more unpleasant than the real thing, for the camera enhances ugliness as well as beauty. Even a tray of surgical instruments becomes a macabre image when its forceps can't be picked up and clicked. For less sensitive readers, however, here is as magnificent a collection of elephantiatic vulvas, ulcerated cervices and frothy vaginal discharges as one could hope to leaf through in the privacy of one's study. Many other specialties have already been included in the *Diagnostic Picture Tests* series, and Professor Tindall's book confounds sceptics who might have thought that our own specialty isn't spotty enough to justify a place The 219 pictures have been collected by the academic department at St Mary's Hospital, Manchester (with a little help from its friends) and to each picture have been added four questions, with answers at the end of the book. The questions are well thought out and the answers are clear and succinct. The book is aimed at undergraduates as well as postgraduates, and although the former may quail at questions on botyroid sarcoma or Bowen's disease, its overall range is well judged—the pictures start with episiotomy and end with Schiller's test. There is also a pleasant smattering of exotica, such as the mutilated hand which reveals an obstetric history to anyone versed in Papuan customs. There are points of controversy (do patients with polycystic ovaries usually have increased vascularity of the breasts?), there are cliffhangers (where is the answer to question 192d?) and there is a cardiotocograph trace which has been printed upside down, but these are minor matters. This pocket-sized collection is a triumph for its authors, their colleagues in the Medical Illustration Department, and the printers.

J. O. Drife

Prenatal Diagnosis of Heritable Skin Disease. Vol. 16 Current Problems in Dermatology (35th Annual Symposium on the Biology of the Skin, Oregon, 1985) and (European Society for Dermatological Research Clinically Orientated Symposium, Oslo, 1986) edited by T. Gedde-Dahl Jr & K. D. Wuepper. Karger, Basel, 1987, 216 pages with figures and tables, £89.10

This beautifully produced 216-page volume contains symposia held in Oregon at the end of 1985 and also at the beginning of 1986. Although designed particularly for dermatologists it includes general principles of prenatal diagnosis, gene mapping, restriction fragment length polymorphisms in linkage analysis and a general catalogue of relevant gene markers divided by chromosomal localization. Particularly informative articles include those by Gedde Dahl on the epidermolysis syndromes and by Byers and his colleagues on the molecular basis of certain inherited collagen defects. At $121.25 the book is extravagantly priced and with the exception of Gedde Dahl's chapter, somewhat under illustrated. Its data are already nearly 2 years old—a distinct disadvantage in such a rapidly moving field. Nevertheless there is a substantial amount of useful information for readers interested in prenatal diagnosis and will therefore be a useful source for dermatologists, paediatricians, geneticists and obstetricians. It is unlikely, however, to be purchased other than as a reference text by departmental and general medical libraries.

F. M. Pope

High Risk Pregnancy: A Team Approach edited by Robert A. Knuppel & Joan E. Drukker. W. B. Saunders Co., Philadelphia, London, 1986, 604 pages with figures and tables, £29.50

The impression gained from the title is that the 'team approach' might involve a multidisciplinary medical team, using particular specialists depending on the 'high-risk' problem. However, a review of the list of authors reveals that over one third of contributors are from the nursing profession. This is not necessarily a drawback, but when the foreword states that 'Nurses and physicians formerly practised their professions in adversarial roles', it suggests that the primary motivation of the book is to draw together a team of obsetricians and midwives involved in high-risk care rather than a team of experts, including midwives, who would be best able to manage specific high-risk problems.

The book is divided into three main sections. The first deals with general aspects of the antenatal period, but mingles physiological adaptations and fetal monitoring with the possible effects of drugs and infections. It lacks any cohesive structure from which to advance into the second section. This deals with complications and delivery, but although problems are discussed in a concise and practical manner, these are generally events which might occur in any pregnancy. Specific problems such as hypertension, diabetes, bleeding and blood disorders are covered and one chapter deals with additional medical complications, but only discusses isoimmunization, asthma, pulmonary oedema and thromboembolic complications. The information provided is standard and of limited value to obstetricians involved in high-risk care. The final section covers post-delivery events such as neonatal resuscitation, parent counselling and grief counselling. The two chapters concerned with counselling are well written, informative and provide the best value in the book.

The editors have tried to write a book for midwives and obstetricians to emphasize the team approach to obstetric care, but the role of midwives in the USA in the management of normal pregnancy and delivery is not yet clearly defined. In the UK and Europe midwives already occupy a central role and are fundamental members of the obstetric team. They may find the book of value in updating their knowledge.

S. A. Walkinshaw

Genetic Aspects of Developmental Pathology. March of Dimes Birth Defects Foundation, Vol. 23, No. 1, 1987 edited by Enid F. Gilbert & John M. Opitz. Alan R. Liss, Inc., New York, 1987, 522 pages with figures and tables, £84.00

Genetic Aspects of Developmental Pathology is based, in large part, on the proceedings of a paediatric pathology symposium held at the University of Wisconsin and contains contributions from some 77 authors. The editors have grouped the 32 papers into nine categories ranging across metabolic and cytogenetic defects, prenatal diagnosis, and treatment teratology and developmental mechanisms of malformation. The relatively high price of the book is reflected in the high quality of reproduction. There are several interesting contributions: Spranger's discussion of recent advances in connective tissue disorders and the structural anomalies of collagen is lucid and valuable as are a number of reviews of rare disorders such as hyperornithinaemia, hyperammonaemia, homocitrullinurea, lissencephaly and hydrolethalus syndromes. The six categories of short umbilical cord reviewed in relation to 15 observed cases will be of interest to obstetricians as will the paper on chromosome examination of 460 embryonic and fetal specimens by Kalousek from a 7-year consecutive series. No fewer than 93·3% of embryos found to have a structural anomaly on examination were shown to have abnormal karyotypes with an overall figure of 59·1% for the series, reinforcing earlier reports of the major contribution of aneuploidy to early pregnancy loss. The elegant studies of cardiac pathology in chick embryos exposed to caffeine and phenobarbital are of interest though, as usual, questions of relevance to man are inevitable.

The overall impression of this book is that the quality of production is excellent as are several of the papers and the editors have tried hard to present these in a coherent fashion. It provides a useful reference source for specific topics and serves its stated purpose of drawing attention to the rapid progress being made in the field of paediatric pathology. The need for specialist consultants in this field grows more obvious with each scientific advance. This is not a volume which most obstetricians would wish to own personally but it may be recommended to local medical libraries.

John Burn

Books received some of which may be reviewed at a later date

Birthplace. Report of the Confidential Enquiry into Facilities Available at the Place of Birth edited by Geoffrey Chamberlain & Philippa Gunn. John Wiley & Sons, Chichester, 1987, 288 pages with figures and tables, £29.50

Parent–Infant Relationships (Volume 4 in the series Perinatal Practice) edited by David Harvey. John Wiley & Sons, Chichester, 1987, 177 pages with figures and tables, £34.95

Principles of Gynaecological Surgery edited by Stuart Stanton. Springer-Verlag, Berlin, 1987, 306 pages with 152 figures, £29.50

Eicosanoids and Reproduction (Advances in Eicosanoid Research) edited by Keith Hillier. MTP Press Ltd, Lancaster, 1987, 241 pages with figures and tables, £45.00

LHRH and its Analogs: Contraceptive and Therapeutic Applications. Part 2 edited by B. H. Vickery & J. J. Nestor Jr. MTP Press Ltd, Lancaster, 1987, 614 pages with figures and tables, £65.00

Handbook of Office and Ambulatory Gynecologic Surgery edited by Philip Darney. Medical Economic Books, Oradell, New Jersey, 1987, 226 pages, illustrated. Available from Medical Economic Books, Box C-779, Pratt Station, Brooklyn, NY 11205–9066 ($24.95) or Quest-Meridien Ltd, 145a Croydon Road, Beckenham, Kent (£23.95+£1.50 postage)

Mammography (Self-Assessment in Radiology and Imaging 3) by Julie Cooke, David M. Hansell & Colin Parsons. Wolfe Medical Publications Ltd, London, 1987, 128 pages fully illustrated, £15.00

Hematologic Problems in Pregnancy edited by David Z. Kitay. Medical Economic Books, New Jersey, available from Quest-Meridien Ltd, Beckenham, Kent, 420 pages with figures and tables, £39 95 (£1.50 postage)

WHO Laboratory Manual for the Examination of the Human Semen and Semen–Cervical Mucus Interaction Published on behalf of WHO by Cambridge University Press, 1987, 67 pages, £8.95

Diagnostic Radiology Exercises edited by Paul R. Goddard. Wright, Bristol, 1987, 200 pages illustrated, £9.95

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British Journal of Obstetrics and Gynaecology
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